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VIRUSES*

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Many of our most common diseases, measles chickenpox herpes febrilis and vaccinia are caused by filtrable viruses. It is desirable that workers who are not actively investigating such disorders as well as those who are so engaged become familiar with this type of disease-producing agent. Therefore through the medium of some general remarks followed by descriptions of specific work conducted in various laboratories I shall attempt to engender a greater appreciation of the problems encountered in this field of research.

VIRUSES IN GENERAL

What are filtrable viruses?[1] Innumerable answers to this question have been proposed but not one as yet has been generally accepted. The unsettled state of affairs in this realm of research extends even to the spelling of words employed in connection with the work. For instance both filterable and filtrable are used, virus, vira and viruses are employed for the plural of virus (there is no plural for the Latin word *virus*) and virucidal, viricidal and virulicidal are used to describe a certain property of antiviral serums, viz the capacity of inhibiting the action of viruses.

The term filtrable virus literally means a noxious agent or poison capable of passing or susceptible of being passed through a filter. By usage it came to indicate certain disease-inciting agents capable of passing through diatomaceous-earth and kaolin filters that hold back ordinary bacteria. After a time however it was found that some very small bacteria and spirochetes also penetrate such filters and not a few diseases because of their characteristics have been placed in the filtrable virus group, even though their incitants are not filtrable or are filtrable with the greatest difficulty. Moreover, filters of plaster of paris have recently been shown to allow the passage of ordinary bacteria while restraining the filtrable viruses. Under these conditions the order of affairs is reversed. Thus, the term filtrable viruses is misleading and confusing. Yet through wide usage and by general consent it now designates a group of active transmissible agents that produce a large number of diseases attacking individuals in practically every realm of plant and animal life, e g, bacteriophagy mosaic diseases of plants, polyhedral diseases of insects, rabies, distemper of dogs, cowpox, foot and mouth disease of cattle pernicious anemia of horses, fowl plague, Rous sarcoma of chickens, herpes febrilis, smallpox, measles and poliomyelitis.

Since many of these diseases are exceedingly common, one naturally asks the question Wherein are they so peculiar that their incitants must be referred to in a noncommittal way as filtrable viruses? At least one of the reasons lies in the fact that no one has conclusively shown that these active agents are capable of multiplication in a medium devoid of living host cells. Hence, they appear to be obligate parasites or in some way to be associated more intimately with host cells than are ordinary pathogenic bacteria. Furthermore no one has yet brought evidence sufficient to convince many workers that the viruses by means of the microscope have been seen or recognized in highly infectious material and also there are indications that at least some of the viruses are of such small size as not to permit of measurement by optical instruments. Indeed Beijerinck in 1898 spoke of the etiologic agent of tobacco mosaic is a contagium vivum fluidum. Moreover some investigators have expressed the belief that certain viruses are inanimate. For example in 1902 Woods asserted that the causal agent of tobacco mosaic is an enzyme and Sanfelice in 1914 reported that the incitant of the contagious epithelioma of chickens, or fowlpox is an inanimate poison, nucleoprotein in character capable of injuring normal cells in such a manner that they elaborate a poison of a similar nature which in turn attacks other normal cells. Thus a hypothesis was presented to explain how an inanimate substance may multiply and indefinitely reproduce itself in series. Similar hypotheses regarding the nature of the bacteriophage and the agent inducing Rous sarcoma have been proposed by various workers in recent years.

If the filtrable viruses continue to resist cultivation on simple mediums in the absence of living tissue, and if they are invisible or of such a nature as not to be recognizable through the sense of sight how then, is one to increase one's knowledge concerning this group of disease-producing agents? At present their existence cannot be determined nor can their identification be established in any manner other than by the evidences of their activity exhibited in some host. Consequently, a study of viruses must be conducted in the host, in the tissues of the host or in emulsions and filtrates of the tissues. To find suitable hosts however is not always easy, and frequently viruses do not produce exactly the same disease picture in different species of hosts. Furthermore it must be remembered that most hosts are subject to natural virus diseases of their own which, if accidentally encountered, may lead to confusion and errors.

From the facts stated, it is evident that workers dealing with viruses are confronted with technical difficulties not encountered in the study of ordinary bacteria that can be seen and grown on artificial mediums. For the study, however, of these peculiar incitants of disease, investigators are not without facilities for pro-

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* Read before the Medical Society of Rochester N Y

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[1] Throughout this paper the terms filtrable viruses and viruses will be used interchangeably

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curing large amounts of them. In fact, suitable hosts, or some of their anatomic parts, e. g., brain, testicle, eye or skin, may be considered living test tubes in which the viruses multiply and leave characteristic evidences of their activity. Frequently 0.2 cc. of infected tissues that have been emulsified and then diluted ten million times contains sufficient virus to produce disease when it is injected into a susceptible host. Cultures in vitro of susceptible tissues also have been found to provide a medium suitable for the multiplication of viruses.

Although the emulsions of infected organs contain large amounts of virus, they should not be looked on as consisting of virus alone, because the protein of the animal or plant tissues represents the major portion of such preparations. In the past, by means of filtration and repeated precipitation, many attempts have been made to obtain the virus of tobacco mosaic, the bacteriophage, the virus of fowlpox, the virus of Rous sarcoma and others in a state of purity. Thus far such experiments have not been entirely successful. There is every reason, however, to believe that in the future much valuable information concerning the nature of these active agents will be derived from this type of investigation.

In spite of the fact that viruses are still obtainable in a state of only relative purity, much can be accomplished with the materials at hand. Prevention of a virus disease does not necessarily depend on the visibility of its etiologic agent or on a complete knowledge of the properties of the agent. Jenner, more than a century ago, without being able to see or to cultivate on artificial mediums the incitant of smallpox, gave a method of preventing the disease. Nearly a hundred years later, still before the filtrable virus group of diseases was recognized, Pasteur, also without being able to see or to cultivate the causal agent of rabies, demonstrated how to combat this malady by means of suitable preparations of the spinal cords of rabbits containing rabic virus.

In 1892 the filtrable nature of the virus of tobacco mosaic was discovered. In 1898 this fact was rediscovered, and the filtrability of the virus of foot and mouth disease was also disclosed. In rapid succession numerous disease-producing agents were placed by various workers in the virus group, and at present, for one reason or another, more than seventy are included. In attempts to control these diseases, the principle of prevention by vaccines prepared from modified or attenuated viruses in infected tissues for a long time was not adhered to vigorously enough. Then came a period of intensive efforts to cultivate viruses on artificial mediums, with the result that many kinds of organisms have been described as the cause of each of the virus diseases. Considerable doubt exists in regard to the relation of such organisms to these maladies. Certainly none of the vaccines made from any of them have been shown to be efficacious in their prevention. The fundamental character of Jenner's and Pasteur's work is being more fully appreciated, and now vaccines are being made from suitable infected tissues. Success with these vaccines, particularly in England, has been reported by workers dealing with foot and mouth disease, distemper of dogs and fowl plague. As new knowledge is gained regarding the proper methods of collecting, purifying, modifying, cultivating and preserving viruses, progress will be made in the control of many of these diseases.

VIRUS III

Some of the difficulties encountered in the investigation of viruses and the diseases caused by them can be emphasized well by a description of some of my work that resulted in the discovery of a new disease inciting agent, virus III. Although the facts to be presented have been reported previously, they appeared at different times in a rather disconnected manner over a period of five years, and a brief orderly account of them now will not constitute a serious repetition.

For reasons that need not be discussed here, I undertook in 1922 the study of chickenpox. The first experiments consisted of attempts to establish the disease in Indian monkeys. These animals were found to be unsatisfactory. Then, as a number of workers had previously shown that rabbit testicles were suitable organs for the multiplication of certain viruses, I decided to inoculate infectious material from patients with varicella into these organs and to make successive testicular passages in the hope of adapting the virus to this host and of obtaining eventually a concentrated virus from which a vaccine might be prepared for the prevention of chickenpox in human beings.

As has been indicated, blood from patients having chickenpox was injected into the testicles of rabbits, and eight testicular passages were made at four day intervals. Experiments were made in eleven series of animals. In five of the eleven series, between the fourth and eighth passages, inoculated rabbits began to have fever ranging from 104 to 107 F. and to show a hemorrhagic reaction in the testicles. When small amounts of testicular emulsions from animals evincing these reactions were injected into the shaved skin or dropped on the scarified cornea of a susceptible rabbit, definite and characteristic changes occurred that were not observed in the controls. The emulsions did not contain ordinary bacteria; emulsions of normal testicles did not cause the reactions; virus heated at 56 C. for fifteen minutes was innocuous; cells affected by the active agent contained typical acidophilic nuclear inclusions; the virus passed through filters; rabbits that had recovered from the disease were refractory to reinfection, and their serum mixed with the virus inhibited its action. The manner in which the testicular material acted, as well as the lesions produced by it, particularly those observed within nuclei of affected cells, led to the belief that the active agent in the emulsions probably was the virus of varicella which had been established in rabbits.

When, by means of the usual tests, attempts were made to demonstrate a relationship between the rabbit virus and the virus of chickenpox as it occurs in human beings, it was found that the two active agents were not immunologically related. Soon it was also noted that a few normal stock rabbits, as well as animals that had recovered from the experimental disease, were refractory to the action of the testicular virus and that their serum neutralized its effect. At about this time Miller, Andrewes and Swift, who in the study of rheumatic fever were also using the technic of repeated testicular passages in rabbits, encountered an active agent that was considered a filtrable virus. Its activity gave rise to reactions and lesions in rabbits similar to those produced by the agent with which I was working, and, on further comparison of the two viruses, their identity became evident.

When it was realized that I was not working with chickenpox virus, that Swift and his co-workers were not dealing with the virus of rheumatic fever, and that both groups of investigators were handling the same virus, I at first thought that in some manner, through the manipulation of the testicular emulsions, a new disease process had been initiated. Consequently, Jillett and I conducted a number of experiments in which repeated testicular passages were made in rats and guinea-pigs. Only negative results however, were obtained. Furthermore, different species of animals, including man (volunteers), were inoculated in various ways with active testicular emulsions but none except the rabbit were found susceptible. Thus, the virus was shown to be highly specific for rabbits. In view of the facts thus far obtained the most likely explanation of the results described seemed to be that in making repeated testicular passages in rabbits a hitherto unknown virus had been encountered in apparently normal animals. To test the validity of this explanation, Andrewes, Miller and Swift using for initial injections blood and testicular emulsions from 'normal" stock rabbits instead of material from patients with rheumatic fever and chickenpox, made repeated testicular passages in rabbits similar to those previously described. After the usual number of passages, they again encountered several strains of a virus similar to the ones previously obtained during the investigations of varicella and rheumatic fever.

The neoplasm of Brown and Pearce arose in the scrotum of a rabbit experimentally inoculated with spirochetes and is propagated in rabbits by means of monthly intratesticular inoculations. It is composed of the kind of cells shown to be susceptible to the action of my virus III. Consequently it occurred to me that the tumor might be an excellent medium in which to study the activity of this agent. In collaboration with Dr. Pearce, I undertook, in the fall of 1924, experiments to ascertain whether virus III was cytolytic or cytotoxic for the tumor cells. Early in the study, the new growth was found to be spontaneously infected with the virus. As the neoplasm has been transferred at monthly intervals over a period of several years, a determination of the date of infection was impossible. We were able, however, to show that the virus was always in the tumor and that it was regularly transferred with it. Furthermore, all the tumor animals became refractory to infection with the virus and their serums developed the power of inhibiting its activity. We were able also to obtain a virus-free strain of the tumor, and animals inoculated with this material, although they developed typical malignant growths, were not refractory to infection with the virus. At various times during the last four years, Dr. Pearce has had occasion to test rabbits carrying the stock strain of the neoplasm and has always found them immune to virus III.

From the time of the discovery of virus III, early in 1923, until September, 1926, when emulsions of tissues containing the active agent were frozen, desiccated, sealed in tubes and stored on ice, approximately 300 testicular passages were made at intervals of three or four days. In January, 1928, the dried virus was removed from the icebox and testicular passages were resumed. In the course of some experiments, intracerebral inoculations with the virus were made in rabbits, and clinical signs of encephalitis, followed by death in many instances, were observed. A histologic study of the brains disclosed a meningo-encephalitis, perivascular infiltration of cells, and a marked degeneration of cells in the cerebrum, cerebellum and upper part of the cord. Many of the involved cells contained typical nuclear inclusions. These observations were unexpected, because shortly after the discovery of the virus intracerebral inoculations of material containing it did not produce in rabbits any symptoms other than a high fever. By means of the proper tests, it has been demonstrated that virus III has not become contaminated with any other known virus, yet one is unable to explain why it now kills rabbits, when originally it did not. In any event, another filtrable active agent has been added to the long list of viruses capable of producing an inflammation of the brain.

Although a new virus that causes a definite experimental disease has been discovered, the spontaneous infection in rabbits has not been recognized. Therefore, no name other than virus III has as yet been given this active agent. The term is used merely for convenience and designates the third strain of the virus encountered with which most of the work happens to have been conducted.

The experiences incident to the discovery of virus III and the results of subsequent work on this active agent emphasize the likely existence of many viruses that are at present unknown, the dangers of making mistakes in working with viruses, the necessity of exercising extreme caution in interpreting results of experiments in this field of research, and the possibility of picking up a virus from the tissues or organs of animals that are, in spite of their normal appearance, carriers of disease-producing agents. This possibility is further emphasized by the work of Cole and Kuttner, who recently demonstrated that approximately 85 per cent of 'normal" adult guinea-pigs carry in their submaxillary salivary glands a filtrable virus capable of causing a fatal encephalitis in young guinea-pigs.

ENCEPHALITIS AS A COMPLICATION OR SEQUEL OF VIRUS DISEASES

Encephalitis, myelitis, encephalomyelitis, meningo-encephalitis and meningo encephalomyelitis are terms frequently encountered in the literature dealing with virus diseases. In fact, the predominant if not the only, symptoms and signs of many diseases occurring under natural conditions are attributable to a direct injury of the nervous system induced by the activity of certain viruses. Such is the case in poliomyelitis, Australian-X disease, rabies, distemper of dogs, and Borna disease of horses. There are other maladies such as herpes febrilis, virus III infections in rabbits, salivary gland disease of guinea-pigs, and vaccinia, the incitants of which under natural conditions do not involve the nervous system. Yet these agents under experimental conditions are highly injurious to nervous tissue. Finally, in the course of or during convalescence from some diseases, e. g., measles, varicella, smallpox and vaccinia, a very small percentage of patients develop signs and symptoms referable to the central nervous system. In these patients the cerebrospinal injury occurs as a rare complication of exceedingly common diseases, and the exact relation of the inciting agents of these maladies to their complications is in doubt. It is this group of unusual and interesting nervous conditions, particularly postvaccinal encephalitis,[2] that I shall now discuss briefly.

In 1922 and 1923, physicians in England and Holland became cognizant of a nervous disorder that occurs as a rare complication or sequel of jennerian prophyitis. To this condition has been given the name postvaccinal encephalitis. Since its recognition ninety-three cases have come to light in England, 124 cases have been observed in Holland, and a few cases have been reported by workers in Poland, France, Austria, Switzerland, Czechoslovakia and America. The onset of the encephalitis, which occurs in the maximal number of cases on the eleventh day after vaccination, is acute, and the course of the disease is rapid. Fever, vomiting, headache, strabismus, varying degrees of clouding of consciousness and occasional paralyses of the upper motor neuron type are some of the signs and symptoms that have been described. The cerebrospinal fluid may or may not present abnormalities. Of the ninety-three British patients, forty-three died, the majority of the fatalities occurred within seven days after the onset of symptoms. Of the fifty patients who recovered, twenty-two were subsequently traced: in sixteen recovery was complete, three showed slight mental changes, one has been subject to convulsions, one had a second attack exactly twelve months after the first, and one developed a hemiparesis. Thus it is evident that the clinical picture presented by postvaccinal encephalitis is unlike that usually seen in poliomyelitis or in epidemic encephalitis.

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[2] A complete review of the subject is given in the report on vaccination to the ministry of health, London, 1928.

Histologic studies of the brains and cords in fatal cases disclosed lesions characterized by a few scattered hemorrhages and a definite perivascular infiltration involving the white matter more than the gray. Some pathologists for a time believed that the lesions were similar to those seen either in epidemic encephalitis or in poliomyelitis. Turnbull and McIntosh, however, were not of this opinion and contended that they found characteristic or specific lesions in postvaccinal encephalitis consisting of perivascular areas of softening situated mostly in the white matter. In 1928 Perdrau reported that by means of appropriate staining methods he was able to demonstrate areas of demyelinization around the vessels of the brain and cord. Furthermore, it is his opinion that these areas are identical with the areas of softening noted by Turnbull and McIntosh. He believes, however, that such areas of demyelinization are not pathognomonic of postvaccinal encephalitis, as they have been observed in certain forms of encephalitis following smallpox, measles and other infectious diseases, and also in early cases of disseminated sclerosis. Perdrau's observations have been confirmed by Bouman and Bok and others, and in view of them it is evident that the pathologic operations in postvaccinal encephalitis also differ from those ordinarily seen in poliomyelitis or in epidemic encephalitis.

Postvaccinal encephalitis is a rare sequel of an exceedingly common procedure, jennerian inoculation. Consequently, one may well inquire whether a similar condition occurs alone or unassociated with other morbid conditions. Moreover, in view of the large number of persons vaccinated each year, one would like to know whether a few cases of postvaccinal encephalitis can be accounted for on the basis of fortuity, i. e., two entirely different disease-producing agents accidentally operating simultaneously yet independently in the same person. In spite of ignorance regarding the cause of postvaccinal encephalitis, the consensus of investigators, based on epidemiologic and statistical data, is that jennerian prophylaxis in some manner is related in most instances to this form of encephalitis. This view is further substantiated by the fact that the evidences of the encephalitis appear at a relatively constant time, eleven days after vaccination. Such an opinion, as is shown later, does not exclude the possibility of an occasional fortuitous overlapping of vaccinia by poliomyelitis or epidemic encephalitis, nor is it incompatible with the fact that a few cases of encephalitis clinically similar to postvaccinal encephalitis and apparently unassociated with any infectious disease have been reported.

A study of the data dealing with the incidence of encephalitis in vaccinated persons discloses some interesting facts. In England the ratio of cases to vaccinations is approximately 1:50,000, while in Holland it is 1:5,000. The difference in the incidence of the disease in these countries may be explained on the basis of the following facts. In England, 63 per cent of all vaccinations are made in infants under 1 year of age, while 66 per cent of the postvaccinal encephalitis occurred in persons between the ages of 5 and 14. In Holland, however, very few infants under 1 year of age are vaccinated. The majority of the inoculations are made in children just under the school age, and 79 per cent of the encephalitis occurred in persons in the third, fourth and fifth years of life. These observations indicate that infants under 1 year of age are relatively insusceptible to postvaccinal encephalitis and constitute a cogent argument in favor of the administration of jennerian prophylaxis during the first year of life. The encephalitis may occur after the first vaccination or following revaccination. The distribution of the disease among the vaccinated population is not uniform, and two instances in which two children in the same family developed symptoms on the same day have been reported. Still there is no definite evidence that postvaccinal encephalitis is contagious.

Although vaccination is in some way related to the encephalitis, the exact nature of the connection between the two diseases is not known. At first, the possibility that the lymph had become contaminated by a neurotropic virus was considered. As many specimens of lymph from a number of sources were used, it is not likely that such a contaminant caused the encephalitis. Furthermore, no extraneous virus has been experimentally demonstrated. Turnbull, McIntosh and a few others believe that the vaccine virus itself is directly responsible for the encephalitis. This opinion is based on the facts that in several instances small amounts of vaccine virus have been demonstrated in the brains in fatal cases, and that injections of vaccine virus into the brains of animals induce an encephalitis similar to that observed in human beings. Most investigators, however, are not in agreement with these workers and contend, in the first place, that they have been unable to recover vaccine virus from the brains in fatal cases; secondly, that the amounts of virus found by Turnbull and McIntosh are not necessarily significant, because Blaxall and others have demonstrated the presence of vaccine virus in the blood, internal organs and brains of vaccinated animals not showing any evidences of encephalitis, and, finally, that intracerebral injections of vaccine virus in animals do not cause an encephalitis of the same nature as that seen following jennerian inoculation in man.

If vaccine virus alone is not the cause of postvaccinal encephalitis and if fortuity does not account for the apparent relation between the two, what then induces this malady of the central nervous system in certain vaccinated individuals? Many investigators have adopted as a working hypothesis the idea that the vaccine virus activates an unknown latent neurotropic virus, or that vaccine virus acting with an unknown agent produces a disease clinically and pathologically unlike that caused by either incitant alone.

Jennerian prophylaxis is an old procedure. Why, then, has postvaccinal encephalitis only recently attracted much attention? Did it occur before 1922? Has a new virus made its appearance? Has a nonpathogenic virus become virulent? Has a mutant arisen from an old virus? Does a similar condition follow other infectious diseases? Have constitutional changes occurred in human beings that increase their predisposition to this type of nervous disease? Most of these questions cannot be answered at present. Although postvaccinal encephalitis has increased in prevalence since 1922, it undoubtedly existed prior to that date. In 1905, a case was reported in France by Comby, another one was observed in 1912 at the London Hospital. Moreover it has been known for a long time that smallpox, varicella and measles are occasionally followed by an encephalitis that is clinically and pathologically similar to if not identical with, postvaccinal encephalitis. For example, Barlow in 1887, reported an instance in which measles was complicated by a disseminated myelitis.

Although encephalitis following measles has been recognized for many years, it seems to occur more frequently now than formerly. Ford,[3] in 1928 reviewed the literature dealing with the nervous complications of measles. He found descriptions of 113 cases, and added twelve new ones in which the brain or cord was involved during or after an attack of this exanthem. As a rule, the onset of the encephalitis or myelitis occurred after the fever had fallen and the rash had begun to fade. The symptoms and signs were indicative of injury to the cerebellum, cerebrum or cord. There was a mortality of 10 per cent. In 35 per cent of the survivors recovery was complete. Frequently, autopsy reports were so incomplete that it was impossible to obtain accurate descriptions of histologic changes in the nervous system. In a number of cases, however, the occurrence of a perivascular infiltration of cells and demyelinization similar to that found in postvaccinal encephalitis was reported.

Following or during the course of antirabic treatment, a few individuals develop symptoms and signs referable to the central nervous system, viz., headache, vomiting, retention of urine, pareses and paralyses. Some of the patients die but many completely recover. The ratio of neuroparalytic accidents to patients given the Pasteur treatment is approximately 1 4,000. The incidence is higher in Europeans and in well educated people than in natives of tropical countries or in manual laborers. There appears to be in some individuals a predisposition to this type of nervous disorder.

The neuroparalytic accidents following antirabic treatment were first observed in 1887. Since that time many opinions have been expressed concerning their nature and cause. It is unnecessary to review the work in this field, because it has been adequately considered in the report of Marie Remlinger, and Vallee to the International Rabies Conference held in Paris in 1927, and also in an article by Stuart and Krikorian,[4] which appeared in 1928. From these reports it is evident that paralysis following antirabic treatment is caused not by rabic virus but by repeated inoculations of the brain tissue carrying the virus. Moreover, similar nervous disorders have been experimentally produced in animals by repeated subcutaneous inoculations of homologous or heterologous normal brain tissue. In what manner these injections induce paralysis is not known. Some workers, however, are inclined to believe that an unknown latent virus is activated. Regardless of the cause of the phenomenon, the pathologic picture, perivascular demyelinization, observed in fatal cases is similar to that found in postvaccinal encephalitis.

In this connection, it is of interest to note that Swift, in his studies of bacterial allergy, observed that a few of the rabbits became paralyzed during the course of repeated intradermal inoculations of streptococci. The majority of the animals completely recovered. Also Julianelle[5] has noticed that a small percentage of his rabbits receiving repeated intradermal injections of dead pneumococci developed paralysis. Unfortunately, no examinations have been made to ascertain whether perivascular demyelinization occurs in this type of paralysis.

Thus, following many infections, and even after repeated injections of supposedly noninfectious material, such as emulsions of normal brain tissue, both in man and in experimental animals, nervous disorders, clinically and pathologically similar, occasionally develop. Moreover, the perivascular infiltration of cells and demyelinization that is common to many postinfectious or postinoculation nervous accidents is also a cardinal feature in the early stage of disseminated sclerosis. Indeed, the pathologic pictures observed under such diverse conditions so strikingly resemble one another that Perdrau has been led to hypothesize for all of them a common etiologic factor. Furthermore, many investigators amplify this conception by stating that the encephalitis may be due to an unknown latent virus aroused to activity by various stimuli such as measles, vaccinia and antirabic treatment or that it results from a "double or combined infection." These are excellent working hypotheses, but very little direct proof has as yet been adduced in their favor. The chief objections to the hypotheses are, first, the necessity of assuming the presence of an unknown latent virus in such a variety of hosts as human beings, dogs and rabbits, and, second, the improbability that such diverse incitants as vaccine virus and normal brain tissue acting in combination with an unknown virus in different species of animals are capable of causing a constant clinical and pathologic picture.

One must remember that vaccinia, measles and varicella are common diseases and that their nervous complications are rare. A more extensive clinical and pathologic study and a more thorough comparison of these nervous disorders should be made before final conclusions regarding their etiology are reached. There is no reason why the virus of measles and vaccinia cannot injure the nervous system. Nor is it unlikely that a fortuitous overlapping of these diseases by poliomyelitis and epidemic encephalitis occasionally occurs. Thus, it is highly probable that encephalitis following infectious diseases may not always result from the operation of a common etiologic factor. If this is true, then the clinical and pathologic pictures observed in these cases should vary. Not all of them are identical. Yet many are, and it is this group that at present particularly interests investigators.

In addition to the hypotheses already presented, I offer another as an attempt to explain how similar nervous accidents may arise under a variety of conditions. As the involvement of the nervous system usually appears late in the course of the diseases under discussion or after repeated injections of such materials as brain emulsions, it is within the realm of possibility that some basic phenomenon, for instance hyperergy, related to the biologic activities that occur in the body on the entry of infectious agents or other types of foreign substances may account for this kind of encephalitis. I am aware of the fact that many workers will object to this suggestion on the grounds that allergy is being too extensively invoked in efforts to explain the manner in which a variety of abnormal conditions arise, and that it is unnatural for the body to react to invasion in a way that will result in injury to itself. In this connection, however, one must keep in mind the fact that allergy or altered reactivity is a universal phenomenon associated with all infections and with the parenteral entry of many foreign materials. Furthermore, not all states of allergy are purposefully protective or beneficial to the body.

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[3] Ford F R Bull Johns Hopkins Hosp **43**: 140 (Sept) 1928

[4] Stuart G and Krikorian K S Ann Trop Med & Parasitol **22** 327 1928

[5] Personal communication to the author

In case some factor of the nature mentioned is capable of producing changes in the central nervous system, why then is encephalitis not more prevalent? The infrequency of these nervous disturbances is not surprising if one considers them accidents dependent either on the constitutional predisposition of certain individuals or on some chance abnormality of the blood vessels of the brain and cord. These ideas may at first appear absurd, but in view of recent work on allergy, they are worthy of serious consideration not only in connection with encephalitis following infectious diseases but also in relation to other obscure nervous disorders.

ANOXEMIA IN PNEUMONIA

MECHANISM OF OXYGEN THERAPY *

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A scrutiny of the problem of pneumonia with the involved physiology of metabolism brings forth a new picture of the malady. Physiologists have opened fields of investigation which bear a close clinical relationship to the problem.

In pneumonia there is an invasion of the body by pneumococci. The body reacts by forming antibodies to combat the invasion. The virulence of the invading organism is variable, both at the beginning of the attack and as the disease progresses.

The rapidity with which the patient builds antibodies varies. In each person there is a variation in antibody formation (resistance) as the disease progresses. A pneumococcus of low virulence attacking an individual possessing rapid antibody formation, is soon stopped (abortive pneumonia). On the other hand, the combination of a virulent organism invading an individual with inadequate antibody formation usually results in a fatality.

Any therapeutic measure that will elevate or prolong resistance, or that will lower the virulence of the attacking organism, will decrease the mortality rate in pneumonia. Since the virulence of the organism cannot be controlled, building and maintaining the patient's resistance must be the physician's aim. The more nearly normal the physiologic activities of the body are kept, the more active will be the resistance and the longer will the body reserves hold out.

In lobar pneumonia there is a variety of frequent pathologic picture. The lung representing the initial seat of the attack presents engorgement closely followed by consolidation. Fever indicates the body reaction to the invasion.

Fever elevates metabolism about 7 per cent for each degree, and this constitutes the first call on the body reserve. Tissue is more rapidly burned, and an increased load is thereby put on the cardiovascular system in supplying the greater demand for food and oxygen: food to furnish power to carry on the body work, and oxygen to support the increased metabolism.

As engorgement progresses to consolidation, the pulmonary absorption area may be decreased to the extent that sufficient oxygen for the support of the increased metabolism cannot be delivered into the blood from an ordinary atmospheric environment.

The patient early develops a pleurisy, the pain of which through the physical and mental excitement that it provokes further increases the body metabolism. The patient manifests the anxious restlessness of air hunger early, with the pleuritic pain inhibiting a fuller respiratory excursion to supply the additional air that is needed. This restlessness is another potent factor in increasing body metabolism. Thus with the arterial oxygen low and the metabolic oxygen demand high, nature reacts by increasing the cardiac output to compensate for the increasing oxygen unsaturation of the blood and body tissues.

Physiology depends largely on oxygen for its support. Any oxygen deprivation interferes with the complete combustion of body wastes, with the inevitable resultant dysfunction of cell acidosis. An acidotic cell cannot utilize the food that is carried to it.

Dextrose furnishes largely the power by which muscle contracts and by which the body carries on. In the execution of this power, through chemical combinations or reactions, dextrose is converted into lactic acid. In the conversion of dextrose to lactic acid oxygen is not required. However, whereas probably five parts of dextrose are thus converted into lactic acid through muscle work, four parts of this lactic acid are reconverted into dextrose to be used again in the repetition of the same process. This reconversion is notably an oxidation reaction. The remaining fifth part of lactic acid is further converted by oxidation into carbon dioxide and water, in which form it is eliminated.

Any interference with the reconversion of lactic acid into dextrose will necessarily rob the body tissues of their sustenance. In pneumonia such interference is *in proportion to the degree of anoxemia present*. Also the same oxygen depletion by its failure to support the reconversion of lactic acid into dextrose will leave deposited within the cell proportionately more waste lactic acid, which cannot be eliminated.

Thus in prolonged partial anoxemia a vicious circle is formed. Assimilation of food is inhibited because of cell acidosis, and cell acidosis cannot be relieved without oxygen. There is an ever increasing demand for oxygen with a progressively decreasing oxygen supply. Therefore nature continues to impose more work on the heart in an effort to provide a compensatory increase of blood to the cell.

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* Sequel to Guedel, A. E.: Oxygen Therapy in Pneumonia, J. A. M. A. 84: 1490-1491 (May 16) 1925.

It must be remembered that every cell of this overworked heart muscle is as sick as any of the body cells that it is trying to serve and that the heart can have no greater sustenance or freedom from accumulated acid waste products than any other body tissue. If the antibody defense is raised to sufficient power to neutralize the toxins of the invading pneumococci before the heart must collapse, recovery is more assured. In pneumonia the immediate problem is the heart. The general problem is the maintenance of physiologic function.

MECHANISM OF OXYGEN THERAPY

By elevating the partial pressure of oxygen in the atmospheric environment of the patient, a greater quantity of oxygen is forced through the alveolar membrane of the lungs into the blood.

The common error in the application of oxygen in pneumonia has been the delay in waiting for the full development of an anoxemic acidosis with dyspnea, cyanosis and a failing heart before beginning its administration. Oxygen to be of value in pneumonia must be applied early. It is easier to maintain a normal physiologic state than it is to retrieve it after it has been reduced by acid intoxication and malnutrition.

The time to begin oxygen in pneumonia is as soon as its application will reduce the heart or respiratory rate or will provide increased rest and comfort for the patient. Oxygen cannot do any harm during the pneumonic period, even in much higher tensions than are commonly employed.

The diffusion rate depends on the difference in partial pressure of gases on opposite sides of the diffusion membrane. It is also influenced by the degree of permeability of the membrane.

The 20 per cent oxygen of atmospheric air forces ample diffusion through the normal lung. In the pneumonic lung the inflammatory engorgement and exudate impairs the activity of the alveolar wall as a diffusion membrane over an area considerably greater than that which is rendered totally impermeable by consolidation. Therefore the 20 per cent oxygen of atmospheric air is not sufficient to pass in requisite quantities through the barrier, and one must aid nature by increasing the partial pressure of oxygen in the environment.

An atmosphere containing from 30 to 50 per cent of oxygen is adequate to eliminate the anoxemic factor in pneumonia. It should be administered as nearly constantly as possible until well after the crisis or until its removal does not produce any sign of anoxemia. The tension or dose is regulated to meet the increased metabolic requirements and the reduced pulmonary absorption activity in each case. The slogan is "Keep the finger-nails pink."

When the application of oxygen is begun the patient should be assured that it is not a method of last resort but a rational therapeutic measure, whether the condition is serious or not. Because of the former inadequate methods of administration, oxygen has become known to the public as a harbinger of death. Without judicious explanation the patient and friends are apt to regard it as the end of all hope.

Oxygen therapy in pneumonia to the abolition of anoxemia accomplishes the following: It provides a higher oxygen saturation of the blood and thus lessens the heart load. It supports the functions of waste combustion and cell nutrition. It supports the aerobic stage of muscle work (reconversion of lactic acid into dextrose) and thus conserves food resources. Finally, the cell, having less lactic acid thrust on it and having oxygen support for the combustion of that which it must eliminate, is kept in a more nearly normal physiologic state.

The same is true of the heart. Its fatigue products are better carried away, its cells are better nourished, and its work is less. Under ample oxygen support the pneumonic heart, as well as the entire human organism, carries on better and longer than would be possible under partial anoxemia. A few hours or days added to the resistance period contributes that much more time for the completion of the antibody defense.

Finally, the intelligent administration of oxygen in pneumonia is physiologically sound. Although it cannot constitute an entire treatment, it is an important therapeutic measure and should be more seriously considered.

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MANAGEMENT OF DRUG ADDICTS IN UNITED STATES PENITENTIARY AT ATLANTA[*]

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A review of our experience with drug addicts at the United States Penitentiary in Atlanta has revealed some interesting observations. Before recounting these it may be helpful to summarize briefly the present accepted methods of treatment of drug addiction.

Like alcohol, morphine seems most abused when most prohibited. It is said that in the East, where it is used commonly in opium smoking, it is relatively much less harmful than here where the ill effects of habitual administration, particularly by hypodermic, are well known. Because of these ill effects and the sufferings of those from whom the drug was withdrawn by the Harrison Narcotic Law, several methods of treating the addiction have been evolved.

In addition to the withdrawal of the drug, all of these methods aim to prevent pain and cause sleep, to promote elimination, to support the circulation, and to improve the self-control as well as the general health of the patient. In the very nature of the case the hospitalization of the patient is usually necessary, both for the technical and for the moral effectiveness of the treatment. The medical treatments consist of modifications of the following: (1) gradual reduction of morphine; (2) administration of one of the atropine series, and (3) vigorous catharsis. The dangers of sudden withdrawal of the drug are always stressed.

The Lambert-Towne treatment is one of elimination, and rapid withdrawal of the drug, with the administration of a mixture of tincture of belladonna, 60 cc., fluidextract of xanthoxylum, 30 cc., and fluidextract of hyoscyamus, 30 cc. Strychnine and digitalis are used if necessary to support the circulation.

The Pettey treatment makes use of catharsis, forced fluids, vapor baths and several drugs, including atropine and scopolamine, for the sedative effect,, with spartein sulphate for support and sodium thiosulphate for a detoxicating agent.

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[*] Read before the Fulton County Medical Society, Nov. 15, 1928.

The Jennings treatment uses ethylmorphine hydrochloride in place of morphine with sparteine sulphate for the support of the circulation. It also stresses hygienic measures and the teaching of self control.

The Sceleth method consists of a preliminary dose of a saline cathartic with the administration of a mixture of scopolamine, pilocarpine, ethylmorphine hydrochloride, cascara sagrada and alcohol, the size of the dose depending on what the patient has been taking. Strychnine is given for support.

Recently the preparation "Narcosan" advocated by Lambert and Tilney has been used at the various penal institutions and hospitals of correction around New York. Narcosan is said to be a solution of lipoid, nonspecific proteins and water soluble vitamins. Its use has been urged on us with the result reported here.

During the past two years at the Federal Prison Hospital we have treated 454 patients for addiction to the use of morphine or heroin, while during the past three years the type of treatment about to be delineated has been followed. In no case has any patient been given a single dose of the drug while undergoing treatment for the drug after entering the institution. Our usual method of treatment is what is known in the parlance of the drug addict or "junker" as "cold turkey." It consists essentially of absolute withdrawal of the drug with an initial dose of mild mercurous chloride and a daily dose of magnesium sulphate. Sedatives such as sulphonmethane and chloral are used freely with simple measures such as sodium bicarbonate and orange or lemon juice to combat nausea. Perhaps our most powerful therapeutic agent is the absolute certainty which the patient has that he will not receive any more "junk," regardless of contingencies. When this is understood there is usually surprisingly little fuss and no remarkable objective indication of discomfort. Usually by the third day the patient's nausea, pains and muscular twitchings, either or all when present, are over, his appetite has returned and he seems much improved. He is discharged from the hospital and put to work as soon as possible so that muscular fatigue may help him to sleep.

*Contraction of Drug Habit**

Bad company		Sickness		Bought but [illegible]	1
Pleasure		Operation		Opium [illegible]	
Curiosity		Injury		Whisky	18
Fun				Syphilis	5
No reason			1[illegible]	In army	11
				Father an addict	1
	1[illegible]3			[illegible]	11
				Third [illegible]	
				Fourth [illegible]	5
				Claims [illegible] [illegible]	1
					111

* Of this total of 4[illegible], four patients are not considered because the habit was broken in jail before their arrival at the penitentiary. Percentages are based on treated cases only.

Because of the commonly understood dangers of circulatory collapse in these cases we have taken careful daily blood pressure readings and four-hourly pulse and temperature observations during the patient's stay in the hospital. Of the 454 patients only 126 showed a variation of either systolic or diastolic blood pressure of 10 points or more. Of these only twenty-two varied 20 points or more and in none were there any symptoms of collapse that were sufficient to cause anxiety. In two cases of marked hypertension there was a drop in the systolic pressure of 56 and 43, respectively, but the pulse rate in both remained within normal limits and these patients were neither in danger nor in appreciable collapse. In the majority of those exhibiting variation in pressure the change was in the nature of a fall in pressure such as might be expected from lying in bed, but in four of the twenty-two patients with a fluctuation of 20 or more points there was a rise in pressure.

The pulse seemed even more constant, in less than forty cases was there a fluctuation of 20 beats a minute and in only ten did the variation exceed 30 beats a minute. These with one exception were patients with pulse of about 100 on entry who gradually regained a normal resting heart pulse of about 70.

Of the 454, seventy-eight or 17 per cent had a temperature elevation of 100 F. for one or more days. This usually occurred on the second or third day and was explainable only by the effects of the treatment except in two or three cases. Of the patients showing fever, thirty-three were among those taking Narcosan, that is to say, 63 per cent of those treated by Narcosan had fever, while only 11 per cent of those treated by the cold turkey method had fever.

Likewise our records show that 160 patients were given sodium bicarbonate to combat nausea, and forty-six of these were in the small group of fifty-two taking Narcosan. The most severe cases of vomiting seen were in those treated with Narcosan. Recently we have been receiving men for treatment who have been treated elsewhere by Narcosan. They agree with us that Narcosan makes the patient more uncomfortable than simple withdrawal and purgation without other treatment. Several of these men have asked that they be allowed to take the "cold turkey" without Narcosan.

As an index to general improvement under treatment and after withdrawal these patients are weighed monthly for three months after discharge from the hospital. Thus we find that of 450 men weighed, eight had neither lost nor gained since admission, 340 men had gained since admission and 102 had lost since admission. The total poundage gained was 4,505 (2,045 Kg.), the total poundage lost 662 (298 Kg.) and the net gain 3,843 (1,730 Kg.). The average gain per man in three months was $8^{54}/_{100}$ pounds (4 Kg.).

These men are interesting as individuals or as a group. Characteristically they lie even when the truth would serve them better, but it may be significant to see how they contract the habit according to their own statements, which are shown in the accompanying table.

It might be suggested that as a matter of fact our method is not actually a sudden complete withdrawal of the drug, since the prisoners during trial and transportation have not been able to get their usual dose of the drug and this is in effect a gradual reduction. In some cases this is undoubtedly true, but on the other hand officers in charge of these patients dispense the drug quite freely and, having only the patient's statement to guide them, may often give doses larger than have been customary. Certain it is that we see many patients on entrance that are suffering from overdosage rather than underdosage.

The situation at the Atlanta penitentiary is unique in that the patient knows that he does not have any recourse to plea or subterfuge which will procure the drug for him while he is in the institution. He can't fire his doctor. This unfortunately is a condition that cannot be duplicated in private practice or in sanatoriums, for it is without doubt one of the most powerful therapeutic agents.

There are of course, certain conditions that present very grave problems such as tabes dorsalis with severe lightning pains, which may have been the cause of the patient's use of morphine Withdrawal leaves these patients miserable and there is no effective substitute for relief of the pains

In thirty-six cases a transient albuminuria was noted during treatment The albuminuria was not persistent except in cases in which organic lesions of the kidney were present before withdrawal of the drug

The figures submitted by the warden of the prison regarding the number of men who are cured by confinement in a penal institution are perhaps not particularly promising According to these figures more than 90 per cent of the men incarcerated for one year or less return to the habit whereas men kept in prison for from three to five years return to the habit in only about 17 per cent of the cases Thus it would seem that long periods of confinement are necessary in order to produce any real beneficial effect on drug addicts

Finally, we can only reiterate that sudden and complete withdrawal of narcotics has in our experience been a perfectly safe procedure Narcosan, instead of being useful, actually makes the patient more uncomfortable during withdrawal We point out too, the tremendous average gain in weight and health after withdrawal and when the patient leads an orderly hygienic existence such as is maintained within the prison walls

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THE FUTURE OF SURGERY*

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History records the conclusions of many distinguished surgeons who were beguiled by the great advances of their day into a false confidence that the zenith had been attained In this twentieth century I believe that it would be safer to err on the side of optimism, and to suggest the advent of achievements beyond our present dreams To avoid this difficult field of prophecy I shall confine myself to a few conjectures on the affairs of the surgeon-to-be

There does not seem to be any rent in the veil that covers the future which even remotely suggests that the labors of the surgeon and his responsibilities are to be lightened If we may make any deductions from the truly remarkable developments during our period, it would seem to be that the future will witness increasing demands on his skill, training and experience How is this supersurgeon to be selected, educated and supported? Much of the responsibility for his qualifications must rest on the leaders of surgery of today

Perhaps we might take stock of present failings before we look forward to the rosy promise of tomorrow The two most serious criticisms of surgery are that unnecessary operations are performed and that poor work is done because of inexperience or lack of ability That these evils are still too prevalent can hardly be denied They may be traced to fundamental defects in the selection of medical students and to inadequate training Liberal financial support of the medical school seems to offer the best form of insurance against unqualified graduates Subsidy to this end by federal, state and private agencies is essential if poor surgery is to be eliminated State appropriations for their universities and hospitals, private endowments and the large gifts by such agencies as the General Education Board and the Rockefeller Foundation have made substantial progress toward this ideal of a liberal financial provision for medical and surgical training

The present internship demanded as a preliminary to graduation in many schools is an indication that a broader application of the principle of supervised postgraduate experience is not far distant The cost of medical education at the present day with its constantly increasing demands is beyond the resources of many aspirants for a medical career Adequate financial aid must be supplied and preferably not in the form of a loan or mortgage on future earnings Such a program would not have socialistic aims—it would be the obvious response to a clear need for a living wage in the final years of prolonged training for a vital service to the public The services of such men, although still in training would have a very definite value

Billroth, writing fifty years ago from Vienna estimated that medical preparation up to the point at which an established income might be expected required about fourteen years and an expenditure of some 24,000 marks He made the following gloomy statement in this connection Any one who is without these material resources should understand that from the outset he will be plunged into a chaos of discomfort and discontent from which he will seldom completely emerge, and that the memory and effects of these experiences will leave their impress on his mood and his character for life" As to the amount of work that might be covered in the usual course, Billroth had no illusions "We must not deceive ourselves and the government as to the amount of actual knowledge, the degree of scientific accomplishment and of technical equipment that can be acquired in four or five years by a man of average talent average energy and average preparation"

It is in surgery that I can most clearly visualize the need for greater training free from the financial demands, which are prohibitive for many who possess the ability and character to render distinguished service to the community The principle of the scholarship or residency with remuneration, developed on broad lines is needed to insure a high standard for practical surgery, as well as to produce research workers and teachers That these greater opportunities should be granted to the promising aspirants is obvious and that their achievements during training should receive an adequate recognition is equally obvious This recognition would probably be most effective in the form of a degree in surgery conferred by a university of good standing, under conditions giving the necessary supervision of postgraduate training

I do not see how surgery can attain the dignity and safeguards that it deserves while the degree of doctor of medicine or a state license to practice is its only guarantee It is the absence of any assurance of adequate special training which I venture to suggest must be remedied in the future, if the foundations of surgery are to stand accredited The aims and accomplishments of the American College of Surgeons to this end are admirable and a definite step in the desired direction I do not believe, however, that the College of Surgeons, or any federal or state agency, can replace the university or relieve it of its responsibility to surgery

We may not have entirely lived down the period when surgery was an industrial guild below the dignity of the physician. For nearly seventy years preceding the middle of the last century the Vienna Surgical Clinic was devoted exclusively to the lay surgeon. In the evolution of medical teaching it is little more than a hundred years since surgery deserted the trades and attained recognition in the medical curriculum. Obstetrics, ophthalmology and other special phases then began to emerge. The development of surgery as a branch of medicine—perhaps an inferior branch—is emphasized because there are still some indications of this attitude in the medical schools.

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* Read before the Southern Surgical Association White Sulphur Springs W Va Dec 11 1928

Up to the present all the activities of the physician or surgeon have been performed under a single degree. This is no doubt a survival of the tradition that the isolated physician must provide aid and assistance in every emergency known to medicine. The granting of this unlimited degree permits the graduate to practice in any special field that he may desire, without regard to whether his assumption of proficiency is based on an adequate postgraduate training, on experience gained by main strength and awkwardness or merely on personal proclamation.

A more definite point of cleavage must in time be established between the broad lines of medicine and surgery leading to a distinctive degree for each. Separation might begin with the internship or postgraduate period or at an earlier stage but the increasing need of longer training demands adequate recognition. The unavoidable limitations of the medical school in the past have made any such program largely unattainable but with the rise of university ascendency in medical education the better appreciation of university ideals and more generous financial support the necessary postgraduate supervision seems a possible development of the near future.

There can be no question that the well nigh universal affiliation of the medical school with established universities will do much to raise the standards of future surgery. There is some reason to believe that the medical school is not the favorite child of the university family group and that it has not as yet attained full favor with the regents. No doubt there are definite reasons for this. The traditions of medical teaching in comparatively modern times have not always been of the highest, particularly when judged from the academic point of view, the cost of the medical department is unquestionably a large one the necessity for adequate hospitals clinics and laboratories involves a heavy expense and many of the medical departments absorbed have furnished vexatious problems in reorganization and have required a large outlay for new equipment. That the university has accepted this task in a commendable spirit and has displayed great energy in the advancement of medical training is everywhere evident. The university is also extending its influence into the field of postgraduate medical training. The gift of prophecy is not required to foresee that the entire field of medical teaching and clinical experience must eventually devolve on the university or that the medical department will become a graduate school. I believe that we may look forward to a further development of university influence in the form of additional medical degrees.

In 'American Universities and Colleges,' 1928 the list of degrees granted is given. Two medical degrees, doctor of medicine and bachelor of science (in medicine) are mentioned. No degree in surgery appears. Degrees in special fields of medicine, such as sanitation, public health and hygiene, are listed. In contrast to this frugality, the law schools confer a baker's dozen.

I do not see how we can reconcile the importance of the present-day responsibilities of the surgeon with the lack of a distinguishing degree. In the history of the early development of medicine, surgery held a very unimportant part, as far as honors were concerned. In the period when medicine was largely a disputation of theory and dogma a medical degree was held in high esteem. The surgeon, however, was ranked more or less as an artisan.

In recent years the degree of doctor of medicine has been shared impartially by the surgeon and by the internist, and only occasionally has it been unworthily bestowed. I do not believe that any degree has ever been more honorably or more unselfishly served. I do not believe that any degree has been held in more general esteem. It is with no thought that this designation should be superseded or replaced that I venture to suggest the need of an added degree in surgery. With the passing of the general practitioner and the general surgeon, some warrant of special training and skill seems inevitable. When this end is attained the surgeon will enter on his duties with more dignity a more certain position and a greater responsibility than now obtains. I believe that we can look forward to the day when all reputable hospitals will demand an adequate degree in surgery from those who operate in their amphitheaters.

In attempting to visualize the training of the surgeon of the future I have no wish to suggest that any educational system will produce finer surgeons than the leaders of today or than we find in the history of the pioneers of our profession. Surgery has always attracted men of the highest character and ability who have outstripped the standards of the teachings of their day. I do believe however that the future will see the gradual elimination of the man of poor ability and inadequate training. We still see in the clinics and postgraduate courses men who are ineffectually endeavoring to secure a belated training denied to them by the struggle for existence. Many of these, of course, lacked initial ability but we may look forward with some confidence to the elimination of these aspiring surgeons at an early stage of training to the great advantage of the individual and of society.

It is my main intention in this rather hasty survey of the future problems of surgery to suggest that the university should stimulate an orderly postgraduate preparation, by providing supervision, opportunity and the proper requirements leading to a special degree. That the future will bring forth some such development seems assured by the remarkable advances we have seen in the standards of medical education—advances largely due to the vision influence and untiring labors of the Council on Medical Education and Hospitals of the American Medical Association.

SUMMARY

Present Conditions.—1. Men imperfectly qualified, even assuming a liberal standard, are doing surgery in every community.

2. Students under present conditions, cannot be adequately trained for the diverse activities that they will inevitably assume after graduation.

3. The public is not safeguarded by the present diploma from a medical school however well accredited it may be since it seems to imply special qualifications as a surgeon or specialist, which it cannot guarantee.

4 The financial burdens devolving on the surgeon-to-be are so heavy that they seriously impede adequate training

Forecast —The growing strength of the university and its ascendency in medical education suggests (1) the graduate school of medicine as the coming standard, (2) the separation of the special fields of medicine prior to the granting of degrees, and (3) university supervision of postgraduate study leading to a special degree

CHRONIC ULCER OF THE LEG

REPORT OF THREE HUNDRED CASES TREATED WITH A MODIFICATION OF THE ORIGINAL UNNA'S PASTE BANDAGE *

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The formation of leg ulcers the causes of which are varicose veins, traumatism, debilitating diseases, syphilis and the nutritive changes incident to age is preceded by vascular changes The most common ulcer, the varicose type, is preceded by a decompensation of the valves situated in the short perforating veins between the superficial and the deep venous systems, these valves are overcome by the weight of the blood column, with resulting stasis and varicosities The nutrition of the skin becomes impaired and the skin becomes eczematous and dark brown from the blood pigment deposits Trauma usually but not always causes the break in the skin, when the skin is once broken, the process of repair is overbalanced by retrograde changes in the tissues, and persistent ulcers result The causes that produce the ulcers perpetuate them

Chronic ulcers pass through three stages (1) extension, (2) a latent phase in which there is neither extension nor repair, and (3) repair In the first stage, pain is the chief symptom There is marked edema and increased local heat, and a definite inflammatory process is set up There is usually breaking down of the skin and superficial tissues, followed by a profuse, thin, irritating discharge During this stage the lymphatics become obstructed and the normal current of the tissue juices is reversed, which adds to the necrotic slough The second stage presents the picture of chronicity, with sharp, well defined edges the margins of which are dark colored, extremely hard and painful The base adherent to the underlying structure is covered with a gray-green tenacious exudate, and no granulations can be seen The discharge has a foul odor and a thick consistency and is somewhat irritating The second stage has been called the indolent or callous ulcer The secondary infection is at its maximum in this stage The third stage is essentially a process of healing, the edges are soft and smooth and are light pink The base is smooth, dark pink granulations can be seen throughout, which bleed easily Pain is not present The discharge is of a serous nature and is abundant In this stage the lesion has been described as the "weeping ulcer" Again there is the lymphatic flow and admixture of tissue juices, with only slight infection

Knowing the pathologic condition described, one must demand in a satisfactory method of treatment the following qualifications care of the active ulcerative lesion and support of the failing circulation of the leg These ends are better attained by some of the advocated procedures than by others 1 Martin's red-rubber bandage has been extensively used and has proved itself one of the better forms of treatment, but its application is difficult and frequently results in destruction of the superficial tissues of the leg 2 The spiral reverse pressure bandage of heavy linen described by Davis is probably the best form of bandage 3 The A-C-E bandage of knit elastic, although widely used, has in my experience proved to be of no value whatever Its chief fault is that, through its loss of elasticity with consequent loosening, it soon becomes ill fitting 4 The rubber stocking made of similar but stronger material lends support to the circulation of the leg and to the ulcer, but after a short period of application there is atrophy of the superficial tissues and general discomfort

All of these methods have in addition to their own individual faults one common failing which is that they do not provide any mechanism for the care of the discharge from the ulcer, the irritating effect of which is a factor of prime importance in the determination of the chronicity of the lesion A satisfactory dressing must allow a free escape of the slough from the ulcer bed and must exert an elastic pressure over the granulating surface, and the dressing material must have an antiseptic property I have used a modification of the original zinc gelatin paste devised by Professor Unna of Vienna and later advocated by Professor Michiels, the original procedure was described in the *Chicago Clinic* of 1900, and more recently has been commented on by Dr Ochsner, who has used it with uniformly good results over a period of fourteen years The paste was originally made by combining gelatin 4 parts, zinc oxide 4 parts, glycerin 10 parts, and water 10 parts This mixture, when cold, forms a homogeneous white mass having a rubbery consistency and a melting point of about 160 F After its preparation it is placed in a double boiler and heated to just above body temperature, at which point it becomes fluid and has a viscosity not unlike that of ordinary paint In this form it is applied with a paint brush directly to the skin of the leg from the base of the toes upward to just below the knee It is allowed to come into intimate contact with the ulcer, no preliminary dressing being necessary A simple spiral bandage without crosses or reverses is applied over the paste, and then more paste is applied over the bandage This is repeated until there is a total of three layers of bandage and four layers of paste The final preparation, when cool, becomes rubbery hard and makes a pressure bandage which, because of its slight porosity, will allow escape of the discharge from the ulcer

Formula for Modified Unna's Paste

Glycerin	1 900 Gm. 1 425 cc
Gelatin	625 Gm
Water	1 900 cc
Zinc oxide	250 Gm
Phenol	1 50% of total volume
	4 675 Gm — 10 pounds (sufficient for seven dressings)

Certain criticisms may be made of this dressing In the first place, it is only slightly antiseptic, and must be changed frequently because of the growth of infecting organisms It is also, because of its high melting point, not flexible enough to be an ideal paste, and it is only slightly porous and does not adequately take care of the discharge from a large ulcer. I have attempted to modify the dressing in such a manner as to meet these criticisms. The formula of the paste that I am using at present is given in the accompanying table. These alterations have seemed to make a much more desirable dressing. The addition of phenol has a threefold beneficial action, as it makes an antiseptic dressing beneath which infecting organisms cannot thrive, it increases the porosity of the paste, and it stimulates the granulating surface. Changing the zinc oxide from 4 parts to 2½ parts increases the flexibility, allows the maintenance of greater elastic pressure and prevents crumbling. The gelatin which forms the basis of the adhesive qualities of the paste has been increased from 4 to 6⅔ parts. This addition lowers the melting point of the paste and increases its flexibility. The modified paste is applied exactly as originally described, except that a figure of eight bandage is carried from the instep around below the malleoli for three thicknesses with *each layer of bandage. Attention is thus directed* toward obstruction of the normal circulation of the foot in order that collateral circulation may be established in the region of the ulcer.

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* Read before the Johns Hopkins Medical Society March 21, 1928

During the past seven months 300 cases of chronic ulcer *of the leg have been treated in my clinic* by this method. Of this number 85 per cent show entirely satisfactory healing; the remaining 15 per cent are still in the earlier stages of treatment and show satisfactory progress. In no case has there been any untoward result. All the patients are ambulatory and are allowed to follow their daily occupations without restriction. A maximum of one hour a week is required for the application of the bandage. The length of time that a single bandage may be left in place depends on the amount of edema and the amount of exudate from the granulating surface. A light gauze bandage may be placed around the more permanent paste bandage and the patient instructed to change the former when necessary. In this manner the exudate which escapes through the pores of the paste will be satisfactorily cared for and the dressing will always present a clean and dry external surface. A paste bandage which has been cared for in this manner has been left in place for as long as twelve weeks, and when at the end of such a period the bandage has been finally removed the ulcer has been found in excellent condition, sometimes completely healed.

The bandage is suitable for use in any climate. When the temperature is very high it may be dehydrated [illegible] with a solution of 85 per cent alcohol [illegible] solution of formaldehyde U. S. P. (6 per cent) [illegible] per cent ether. This solution is applied

BLOOD PRESSURE AND RESPIRATION

HYPERVENTILATION AS A TREATMENT FOR HYPERTENSION

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For some time in a few cases of hypertensive disease of the so-called essential type I have succeeded in maintaining marked reductions of blood pressure levels by deep breathing exercises. Clinical observations in these cases seemed to exclude mere coincidence, and a study of the literature revealed an abundance of direct and inferential data in support of my experiences, which in themselves are too few to permit any conclusions. Physiologic and clinicopathologic data on the correlation between respiration and circulation make it plausible that systemic blood pressure should be profoundly influenced by respiration. In the light of these recently acquired data on the correlation existing between respiration and circulation it is easy to explain why hyperventilation should reduce systemic blood pressure. In this review of the subject I believe I present proof that hyperventilation is a logical treatment of hypertension. Only the small amount of clinical material and clinical evidence has delayed this publication until now.

In the meantime Tirala[1] of Bruenn, in the section of internal medicine at the Ninetieth Congress of the German Association of Natural Scientists and Physicians, held at Hamburg in September 1928, has reported marked alleviation of pathologically increased blood pressure by systematic deep breathing exercises as observed in a large clinical material over a period of several years. This prompts me to delay no longer but to call the procedure to the attention of all who have the opportunity to put it to the test of large scale experience.

PHYSIOLOGIC CONSIDERATIONS

The profound influence exerted on the systemic blood pressure by the respiration is evident from the following set of physiologic phenomena. Systemic blood pressure undulates with the phases of the respiratory cycle. Forced respiration, or hyperventilation, causes a sharp drop in systemic blood pressure. The respiratory experiment named after Valsalva is known to cause almost total collapse of the circulation. According to Starling[2] the respiratory undulations of systemic blood pressure are due to the fact that inspiration has a tendency to retard the return of the blood to the left side of the heart. What hyperventilation does to the blood pressure has been demonstrated repeatedly since the acapnic shock experiments of Yandell Henderson. The most recent experiments of this type have been carried out by Vincent and Thompson[3] on a large number of normal subjects under a variety of experimental conditions. It was concluded from these experiments that hyperventilation—not extending to the point of apnea—produces a 25 per cent drop in the systemic blood pressure. The Valsalva experiment has recently been studied by Buerger with a large number of medical students as subjects. Tracings of respiration and blood pressure were obtained and intrathoracic pressure was simultaneously measured by letting the subject expire with full force against a manometer after he had taken a few deep inspirations. It was found that as soon as an intrathoracic pressure of from 16 to 20 mm. of mercury was recorded systemic blood pressure at first rose a few points for a few seconds and then followed an abrupt and sharp decline of from 80 to 100 mm. in proportion to the rise of the intrathoracic pressure. Buerger[4] concludes that the distending lung retards and finally shuts off circulation in the lesser circulation. Yet Blumgart and Weiss[5] have demonstrated by direct measurement of the velocity of blood flow through the lungs—a measurement from arm to arm by an ingenious technic—that under pathologic conditions of pulmonary distention the pulmonary circulation time is not prolonged. These workers have measured the velocity of blood flow from arm to arm in a series of patients with chronic high grade emphysema and have found that under these circumstances pulmonary circulation time is rather shortened than prolonged.

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[1] T[illegible] L [illegible] Ninetieth Congress of German Association of [illegible] 9 3 [illegible] Klin Wchn[illegible] 1928 [illegible] 4

[2] Sta[illegible] E[illegible] Principles of Human Physiology, Philadelphia, Lea & Fe[illegible] 19[illegible]

[3] Vincent S[illegible] and Thompson: J[illegible] J Phys[illegible] 66: 3[illegible] ([illegible] 9[illegible])

It is known from other pathologic conditions, as well as from experimental evidences that pulmonary distention as such facilitates circulation in the lungs. Hyperventilation in exercise is known to increase the amount of blood rushing to the lungs for arterialization to many times the normal. This is known to be accomplished by the tremendous emphysematous distention of the lungs, in which all its tissues, including its vessels, greatly increase their capacities. While it is true that exercise momentarily raises systemic blood pressure, it has recently been emphasized by Abrahams[6] that the old notion that increased blood pressure is due to exercise is all wrong, the tendency to lowered systemic blood pressure in athletic persons having been demonstrated.

Without further discussion of these physiologic data, the following facts may be recognized. Hyperventilation—pulmonary distention—enhances the blood flow within the lung; it increases the amount of blood circulating within the lung. At the same time hyperventilation apparently retards the return of the blood to the left side of the heart; it prevents a considerable portion of the blood from returning to the left side of the heart within the unit of time necessary to maintain the normal output from the left side of the heart. Reduction of the left cardiac output and a fall in the systemic blood pressure are the result of hyperventilation. From all appearances the amount of blood in question is being retained within the lungs in the distended vascular bed of the lesser circulation.

CLINICOPATHOLOGIC CONSIDERATIONS

Janeway mentions three factors in the production of increased blood pressure; increased volume of blood, increased peripheral resistance, and increased cardiac energy. Increased volume of circulating blood as a pathogenic factor in hypertension has suggested itself strongly to physicians of all times. Plethora sanguinis—the old ghost of medical ages long past—is by all appearances making its reentry into clinical medicine right now. Ever since Barcroft[7] demonstrated the vastly important function of the spleen as a blood reservoir, the effect of blood depots on general circulation has come to loom large in present-day clinical conceptions. Eppinger[8] followed with investigations of other organs as blood depots and disturbed depot function, increased circulatory volume and disturbed distribution of circulatory blood volume are being considered as underlying causes of many clinical conditions of disturbed circulation. Eppinger made a study of the circulating blood volume in a series of hypertensive patients and demonstrated the increase of circulating blood volume in all of them. He also found that contrary to the great increase normally seen on heat application and exercise, these patients show little or no increase of circulatory blood volume on heat or exercise. A similar increase of circulating volume was found by Wollheim in decompensating hypertensive patients. Wollheim[9] even sees the cause of the decompensation in this increased circulating blood volume which he attributes to disturbed depot function. All this is supported by the experience of ages that bloodletting relieves the symptoms of hypertension and is capable of averting its dangers. Bloodletting has been done for centuries, and is still being done in these conditions ever so frequently and continuously for periods extending in some cases over many years. Grothusen[10] studied the effects of bloodletting orthodiagraphically, and demonstrated marked reductions in the size of the heart following bloodletting. With the recent investigations of Eyster[11] showing that increased blood volume is the most frequent cause of cardiac hypertrophy, the likelihood of hypervolemia as the outstanding pathogenic factor of hypertension becomes more probable than ever.

However strongly hypervolemia suggests itself as the cause of hypertension, one cannot overlook the fact that reliable American investigators, such as Geraghty and Rowntree, could not substantiate the observations of others as regards hypervolemia in hypertensive patients. However, the technic of blood volume determinations is in its infancy as yet, and the results are far from reliable even at the hands of the most careful investigators. It would be unsafe to base clinical assumptions on it, either pro or contra. Furthermore, hypervolemia is not even a condition sine qua non of hypercirculation, which may exist without an absolute increase of the circulating blood volume if a part of the circulation bed is short circuited in such a manner as to cause the given amount of blood to circulate within a reduced vascular area. The greater part of the cardiovascular surface area consists of the huge capillary nets throughout the body. The single capillary area in which changes of surface and capacity are of such nature and dimensions as to be likely to affect the entire circulation is that of the lesser circulation.

As is known the lesser circulation has the widest capillaries, in greater abundance than any other part of the body. Of this capillary area Starling has demonstrated such variations in capacity as are unique in the body. "At inspiration it may hold one twelfth, with compression it may be reduced to hold one sixtieth, of the total blood volume." Starling remarks that "such changes may exercise considerable effect on systemic blood pressure. The distensibility of the lung capillaries may play an important part in enabling the lungs to act, so to speak, as a reservoir for the left side of the heart." With this statement Starling defi-

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[4] Buerger, M.: Klin. Wchnschr. 5: 18 19, 1926.

[5] Blumgart, H. L., and Weiss, Soma: J. Clin. Investigation 4: 173 (June) 1927.

[6] Abrahams, A.: Lancet 1: 429 (March 3) 1928.

[7] Barcroft, J.: J. Physiol. 60: 443 (Oct.) 1925.

[8] Eppinger, Hans, and Schurmeyer, A.: Klin. Wchnschr. 7: 777 (April 22) 1928.

[9] Wollheim, E.: Klin. Wchnschr. 7: 27, 1928.

[10] Grothusen, G.: Med. Klin. 23: 1615 (Oct. 21) 1927.

[11] Eyster, J. A. E.: Experimental and Clinical Studies in Cardiac Hypertrophy, J. A. M. A. 91: 24 (Dec. 15) 1928.

excursions, high blood pressure is invariably reduced. Thus are explained the "splendid results" obtained by drinking cures at many spas to which hypertensive patients flock annually. In the French literature it is pointed out that retention of old feeding habits by persons retiring to a sedentary life after an active past frequently leads to hypertension. Emphasis is put on the hypercirculation thus maintained in disproportion to the downward tendency of other functions in the body.

In relating my own clinical experiences I can be brief. For nearly two years I have been observing a number of hypertensive patients and have been struck with the fact that they were all poor breathers. They showed what I came to call "the low breathing habit." The features of this phenomenon are a markedly reduced respiratory rate, pulmonary expansion far below the average, and diaphragmatic excursions of a very restricted type, without any evidence of pulmonary disease to account for it. These patients gave the impression of having established themselves at a pulmonary capacity—probably the mean of their already reduced respiratory need—so that their respiratory function could take place within a narrow range of respiratory excursions and even at this point they needed only a reduced number of respiratory cycles. I found, however, that it was possible to correct this anomaly by a concentrated effort at deep breathing exercises carried out repeatedly, daily, over a period of several months. Considerable increase of spontaneous pulmonary expansion could be obtained in some cases after several weeks of conscientious breathing exercises. Reductions of blood pressure levels—an average of 30 per cent of the pathologic surplus—were thus obtained and maintained, in some of the cases for nearly two years. In some cases it was necessary to interrupt the patient's life work temporarily for the purpose of carrying out a successful regimen. I may add that none of the patients have thus far reached the point of normal respiratory expansion or normal blood pressure level. In some of the cases hypoventilation is still a marked feature, though improvement is noticeably progressing. Some of these patients had other symptoms associated with hypertension, especially were gastro-intestinal symptoms complained of, all of which yielded promptly to the treatment.

If the available data are to be correlated, one must first realize that physicians are as yet far from being able to integrate the pathologic and clinical sequence of events. These data, however, enable one to construct the broad outlines of a conception of the clinicopathologic course in the development of hypertension. I believe that this conception has sufficient theoretical basis, receiving, as it did, considerable practical confirmation, too, it warrants discussion and deserves serious consideration.

Hypertension is overwhelmingly the disease of the second half of life. In spite of the fact that little more than the increased blood pressure was known about it, it was felt that it represented more than a symptom. Physicians have always held that it was the expression of a fundamental change in the vital economy, it has always been considered a disease. As such, it was marked early as the disease of the involution period of life. It is also known that with the second half of life metabolic processes of the organism begin their down grade, they are beginning to slacken. Probably the great change in the internal secretions, the menopause, is responsible for this metabolic involution process, which cuts down the oxygen consumption of the organism. Respiratory function soon adapts itself to this reduction of the oxygen consumption, respiration becoming gradually restricted. Many of these individuals have a tendency to overfeed and thus enhance circulation, but even in those with normal circulation this is apt to continue on the same level even after the metabolic processes have slackened down. A disproportion between circulatory and respiratory function will thus arise, the first being considerably in excess of the latter. A condition of "relative hypoventilation" may thus be assumed to develop in middle life in a great number of persons destined to become hypertensive.

The mechanism by which such "relative hypoventilation" would start a chain of events leading to hypertension is, according to my conception, as follows: Normal pulmonary expansion entails a definite extent of capillarization—spreading out on a capillary area—of the blood entering the lungs with every heart beat. The greater the capillarization—pulmonary expansion—the greater will be the amount of blood momentarily contained within the lungs. As is known, a normal extent of capillarization maintains in the lesser circuit a blood depot amounting to about one fifth of the total volume of circulating blood. This depot function therefore serves the purpose of regulating the distribution of the circulating blood volume between the lesser and the greater circulations. Relative hypoventilation goes with reduced capillarization in the pulmonary circulation, it tends to interfere with the depot function of *the lesser circulation and therefore profoundly disturbs* distribution of the circulating blood volumes between the two circuits. The result of such a disturbance will first be felt by the arterial system, which must receive and take care of the overload of blood.

If one considers that this overfilling of the arterial system arises in persons who are stepping into the involution period of life, whose blood vessels are losing their capacity of adapting themselves to variations of their contents, all subsequent events become understandable. It is quite obvious that if such a condition of overfilling must be kept up constantly for any length of time, the effect of hypercirculation will be a tissue hyperplasia throughout the overloaded cardiovascular bed, from the left side of the heart to the smallest of arteries. The hypertrophy of the left side of the heart and the thickening of the arterial walls will progress in proportion to the gradually decreasing depot function of the lesser circuit, i. e., the increasing overload. Thus arises the "hypertonia of the vascular wall," which, as has been pointed out by Pal,[20] would in itself be sufficient to cause hypertension even if the cross-section of the vascular bed as a whole remained the same. The reason for this is found in the decreased vascular distensibility, which is caused by the thickening of the vascular wall. Janeway's second factor in the production of high blood pressure, increased peripheral resistance, is here. To overcome this, the left ventricle will go into still greater compensatory hypertrophy. Janeway's third factor, increased cardiac energy, steps in finally to close the chain. It is therefore logical to conclude that "relative hypoventilation" started a chain of events, a vicious circle, the consequences of which are growing in geometric proportions. It is also logical to conclude that cutting this vicious circle by increasing respiratory function will reestablish depot function in the lesser circuit and bring about proper distribution of circulating blood volumes between the two circula-

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[20] Pal, J.: Med. Klin. 24: 123 (Jan. 27) 1928.

same nature These investigators stress the probable relationship of ventricular tachycardia and coronary disease and call attention to the fact that dogs whose coronary arteries have been ligated very commonly develop ventricular tachycardia as a result of this manipulation Major and Wahl[5] report a case of ventricular tachycardia in which focal inflammatory areas were found in the ventricular muscle together with some disease of the coronary arteries One of the cases reported by Butterfield and Hunt[6] which exhibited a ventricular tachycardia showed extensive changes in the interventricular septum with vascular connective tissue formation In contrast this arrhythmia occurs on rare occasions in young people in whom there are found no signs of heart disease and in whom the only cardiac symptoms present are those associated with the tachycardia, namely palpitation giddiness, faintness and at times mild dyspnea Case 1 and the case reported by Scott[2] are instances of this The patient reported by Jones and White[7] showed only slight cardiac enlargement and at no time did he have any symptoms of heart failure It is significant that whereas the form of arrhythmia that occurs in patients with badly affected hearts is looked on as a possible precursor of ventricular fibrillation and hence as a very serious disorder it may occur in young people in whom there is no evidence of heart disease, and in whom ventricular fibrillation is not even considered as a likely complication

In the second place, paroxysms of ventricular tachycardia in some instances have been induced by very slight exercise and in others exercise has abolished the attacks Finally, quinidine, which is known to bring about cessation of these attacks, has also been thought to cause them In treating patients with auricular fibrillation, Levy[8] secured in several instances electrocardiograms which he interpreted as showing ventricular tachycardia His published curves are suggestive of defective conduction of supraventricular impulses They do not fulfil all the postulates of ventricular tachycardia cited by Robinson and Herrmann[4] although one case looks much like a real instance of this arrhythmia[9] Other writers, including Lewis[10] and Oppenheimer and Mann,[11] note the possibility of ventricular tachycardia developing in cases of auricular fibrillation treated with quinidine and consider this development an indication for the immediate discontinuance of the drug All of these paradoxic observations stress the fact that our knowledge of the exact cause and nature of ventricular tachycardia and the role of quinidine in its treatment is still very limited

However dangerous the procedure may be considered, a number of cases of ventricular tachycardia have been *successfully treated* with quinidine when other means of therapy were of no avail In the case cited by Scott[2] the patient was made free from her attacks and remained so on a daily dose of 0 2 Gm Cases similarly treated have been cited by Barrier,[12] Gilchrist[13] Jones and White[7] and Wolferth and McMillan[14] We report here the case histories of ten patients treated in the hospital or by one of us in private practice All of these patients received quinidine either by mouth or intravenously In eight of them it produced a specific return to a normal mechanism In one of the others there was temporary slowing of the heart rate, and in the last one no effect was produced The patients were all over 40 years of age There were eight men and two women In one instance (case 1) there was no evidence of organic heart disease In another (case 2) the patient had chronic cardiac valvular disease with mitral stenosis The remaining eight were suffering from coronary thrombosis In these the ventricular tachycardia first appeared at intervals varying from twelve hours to fourteen days from the time of their acute attack following coronary occlusion Though seven of the patients died in none of them did we feel that death was the result of quinidine intoxication In fact, quinidine had been entirely discontinued for some days in most of the instances before death occurred One patient died of lobar pneumonia, one of a cerebral embolus, another of rupture of the heart, and the remaining four of coronary thrombosis

There are two points that should be noted here In the first place ventricular tachycardia when occurring as a complication of coronary thrombosis, in itself a grave condition, presents a very serious situation It is obvious in such instances that the severely injured heart cannot maintain for long a rate of from 150 to 200, so that anything that can be done to favor the return of a normal rhythm is worthy of trial The gravity of the condition warrants the risk of giving a drug which we know is dangerous but which at the same time may be life-saving Secondly, at times it may be necessary to give the drug in very large doses to secure and maintain the desired effect The exact dosage is a variable matter and must be determined by trial and error We usually begin with 0 3 Gm of quinidine sulphate and repeat the dose every four to six hours raising it 0 1 or 0 2 Gm each dose or in urgent cases even more rapidly In one instance (case 6) it was necessary to give 1 5 Gm five times within twenty-four hours before a normal rhythm was established less than this amount being ineffective After the return of the normal rhythm the patient is kept for a variable length of time on 0 2 or 0 3 Gm three times a day or oftener if necessary In case 2 it was found after repeated trials that a daily dose of 2 4 Gm was necessary to maintain a slow heart rate and the patient was able to continue on this dosage for months without ill effect The amount necessary must be determined *according to the individual's reaction and condition*

Obviously this method of treatment would have a very limited use if the disturbance for which it is given could not be recognized at the bedside Whereas formerly it was thought that ventricular tachycardia could be identified only by electrocardiographic means, there are now available simple criteria that can be applied by any practitioner in the sickroom[15] The three points that distinguish ventricular tachycardia from other forms of rapid heart action are: First, the rhythm is rapid and is essentially regular but slight irregularities can be detected. Second, the quality of the first heart sound varies in intensity in some of the cycles. Third, attempts at vagal or ocular pressure prove ineffective in slowing the tachycardia.

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[5] Major R H and Wahl H R Paroxysmal Tachycardia Associated with Focal Myocarditis J A M A **86** 1125 (April 10) 1926

[6] Butterfield H G, and Hunt G H Observations on Paroxysmal Tachycardia Quart. J Med **7**: 209 (April) 1914

[7] Jones T D and White P D Paroxysmal Ventricular Tachycardia Report of an Unusual Case Am Heart J **2**: 139 (Dec.) 1926

[8] Levy R L Clinical Studies of Quinidine II Alterations in the Cardiac Mechanism After Administration of Quinidine to Patients with Auricular Fibrillation with Considerations of Certain Toxic Effects of the Drug Arch Int Med **30** 451 (Oct.) 1922

[9] Levy R L Clinical Studies of Quinidine III Some Results of the Quinidine Treatment of Auricular Fibrillation New York State J Med **22**: 276 (June) 1922

[10] Lewis Thomas The Value of Quinidine in Cases of Auricular Fibrillation and Methods of Studying the Clinical Reaction Am. J M Sc **73** 781 (June) 1922

[11] Oppenheimer B S and Mann Hubert Results with Quinidine in Heart Disease *abstr J A M A* **78** *1752 (June 3) 1922*

[12] Barrier C W The Use of Quinidine in the Treatment of Ectopic Rhythms J A. M A. **89** 742 (Sept 3) 1927

[13] Gilchrist A R. Paroxysmal Ventricular Tachycardia A Report of Five Cases Am Heart J **1**: 546 (June) 1926

[14] Wolferth C C and McMillan T M Paroxysmal Ventricular Tachycardia Report of One Case with Normal Type of Auricular Mechanism and Three with Auricular Fibrillation Arch Int Med **31** 184 (Feb) 1923

[15] Levine S A The Clinical Recognition of Paroxysmal Ventricular Tachycardia Am Heart J **3** 177 (Dec.) 1927

These clinical experiences, which are detailed in the accompanying case histories, seem to prove quite conclusively that quinidine sulphate has a most beneficial effect that is almost specific in abolishing and inhibiting the rapidity of the beat due to the ventricular tachycardia. When this disturbance in the heart's mechanism develops in patients who have nothing or very little wrong with the structure of the heart, the quinidine can serve to regularize the rhythm and thus do away with palpitation, which may be either annoying or even incapacitating. When the tachycardia occurs in coronary thrombosis, quinidine will be effective in controlling only this particular complication of the disease. Because the underlying condition here is most grave and is frequently followed by disastrous complications, such as heart failure, embolus formation or rupture of the heart and because it is of itself often fatal apart from the development of ventricular tachycardia, it would not be expected that all or even most patients would recover. It has been our impression that ventricular tachycardia occurs in the more severe instances of coronary thrombosis. The clinical experience in which one sees a moribund patient improve abruptly and most dramatically after the return to normal rhythm following quinidine is sufficient evidence of its great therapeutic value.

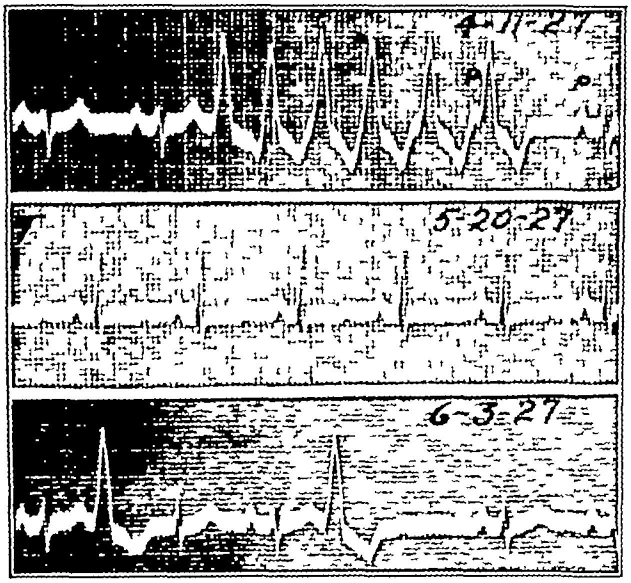

Fig. 1 (case 1).—First tracing shows a short paroxysm of tachycardia made up of consecutive extraventricular systoles, note the regular and independent P waves. Middle tracing shows complete disappearance of the irregularity under quinidine. Lower tracing shows return of occasional extrasystoles under insufficient quinidine.

REPORT OF CASES

Case 1.—E. B., a woman aged 41, complained chiefly of fluttering of the heart. At the age of 32 she had had influenza, at which time the heart beat was quite irregular. Her physician had her keep an ice-bag over the precordium. Four years later she began to have a good deal of nervous indigestion and with it the heart "thumped dreadfully." This continued for a while and then disappeared. During the past year, as the result of caring for her invalid mother the patient became nervous again and the palpitation of the heart returned. She did not have any dyspnea, cough, chest pain or nocturia. She had never had rheumatic fever, chorea or scarlet fever, although she had diphtheria at the age of 7. The family history was not remarkable. An examination, April 11, 1927, showed her to be well developed. The lungs and the abdomen were normal. The blood pressure was 122 systolic and 96 diastolic. The heart was not enlarged. There were no murmurs. The action was irregular. Frequent runs of rapid regular beats were heard (fig. 1), then sudden pauses with a normal regular rhythm and occasionally single extrasystoles. There was no peripheral edema. The urine was normal. At this time the patient was told that she was not suffering from any serious disease, but merely that she had a nervous irregular beat. She was not given any medication. One month later she was again examined and the condition was found to be exactly the same. Palpitation was continuously troubling her. May 13, she began taking 0.4 Gm. of quinidine sulphate three times daily. On the second day of this treatment, all palpitation disappeared (fig. 1). The following month the dose of quinidine was reduced to 0.2 Gm. three times daily and the palpitation returned to some extent (fig. 1). She then took the larger dose and the heart action was regularized. In this case there was no doubt as to the specific controlling influence of quinidine on the irregularity of the heart.

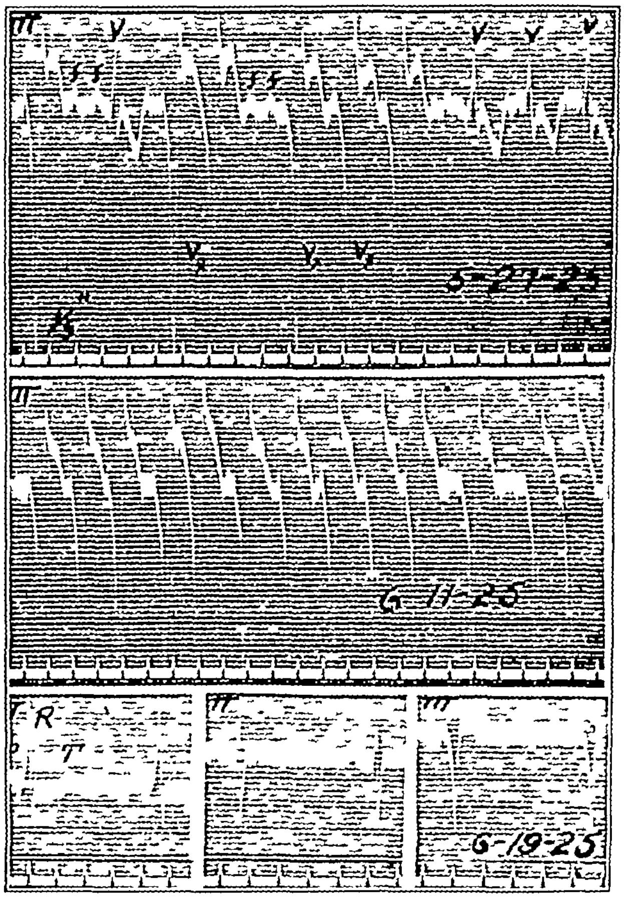

Fig. 2 (case 2).—First tracing (lead III) shows auricular fibrillation (f f) and ventricular tachycardia (Vx); note occasional supraventricular beats (V); rate, 144. Middle tracing (Lead III) shows rapid ventricular tachycardia; rate, 183; note absence of supraventricular beats and increased rate as the result of digitalis. Third set of tracings shows three leads with a normal heart mechanism.

Case 2.—A. L., a man, aged 48, complained chiefly of shortness of breath. There was no previous history of chorea, rheumatic fever or tonsillitis. At the age of 21 he fell to the floor after strenuous physical exertion and noticed then for the first time that his heart was beating rapidly and irregularly. Following this he had no unusual symptoms except that his heart often seemed to beat peculiarly when he was troubled with coryza or pharyngitis At such times he was mildly dyspneic For the past few years the patient experienced increasingly frequent attacks of nocturnal dyspnea, lasting usually one half hour, and ending gradually Severe coughing, productive of mucus, accompanied these attacks For several weeks before examination there had been attacks of stabbing pains low down in the left side of the chest unrelated to exercise or emotion One severe attack of "fluttering' and dyspnea ten days before admission had been uninfluenced by full doses of digitalis An examination, May 27, 1925, showed him to be somewhat overnourished and slightly dyspneic The heart was moderately enlarged and showed an irregular rhythm, a rate of about 150, a faint apex impulse, and a slight apical thrill apparently systolic in time The first heart sound had a rumbling quality No definite murmurs were heard Electrocardiograms (fig 2) showed auricular fibrillation and ventricular tachycardia The lungs showed a few congestive rales, and the liver was enlarged Otherwise the examination was not significant The blood pressure was 90 systolic and 80 diastolic On 2 7 Gm of digitalis given during eight days, the heart rate increased with a wide pulse deficit Electrocardiograms (fig 2) showed a rapid ventricular tachycardia and a rate of 183, without supraventricular beats Numerous tracings taken during this time showed that auricular fibrillation continued On the eleventh day the patient was started on quinidine sulphate 0.2 Gm being given twice, thereafter each dose, given three times a day, was increased 0 1 Gm daily until he received 0 8 Gm., when the rhythm was found to be regular, the rate 73 and the electrocardiogram normal (fig 2)

Examination at this time revealed evidence of mitral stenosis The maintenance dose was not known, but it was found that while 0 6 and 0 7 Gm were given three times a day, the rapid ventricular rate still returned On 0 8 Gm three times daily the slow normal rate was satisfactorily maintained and the patient continued on this dosage without ill effect He resumed his position and continued to work until April 1926, when he contracted lobar pneumonia which resulted fatally At the time of the last entry the heart action was slow and regular Autopsy showed lobar pneumonia and mitral stenosis[16]

Case 3—A D, a man, aged 64, seen in consultation at his home, Jan 28, 1927, because of a severe heart attack, had had a somewhat similar, but much less severe, spell three years before. For the past six weeks he had had sternal constriction on walking He had had mild diabetes for ten years Thirty-four hours before he was seen, after unusual effort and excitement, he felt a terrible pressure over the sternum 'like a load of 2 tons on the chest" He broke out into a cold perspiration, there was a feeling as if the heart were bursting On examination the patient appeared muscular and slightly cyanotic The heart was slightly enlarged, the sounds were distant, the action was regular and the rate was 110 There was a very slight apical systolic murmur Many rales were heard at both bases There was slight liver tenderness in the epigastrium The blood pressure was 102 systolic and 80 diastolic The temperature was 101 orally and 103 rectally The whole picture was typical of coronary thrombosis During the following few days his physician noted on several occasions a rapid, irregular heart action, with the rate about 150, which disturbance must have been transient, as during the intervals the rate was always 110 and regular The patient was given full doses of digitalis, but his condition had grown distinctly worse He became irrational and had to be catheterized and the pulse at times was almost imperceptible The blood pressure reading was 80 systolic and 70 diastolic

February 2, when the patient was seen by one of us, the heart rate was found to be 155, the action was regular with an occasional skipping At this time the exact type of the disturbance of the mechanism of the heart was not known At first it was thought to be due to auricular flutter, and therefore more digitalis was given intramuscularly without any effect. February 5, when it was found that the condition was unchanged, the question arose whether the extremely rapid rate was due to digitalis poisoning, producing complete heart block with rapid ventricular rate One such case we had previously seen It suddenly became apparent that the disturbance was most likely a paroxysmal ventricular tachycardia, for there were slight irregularities in the rhythm, which was otherwise very regular The quality of the first heart sound varied at times, and repeated attempts at vagal and ocular pressure failed to stop the tachycardia Finally, digitalis was in no way helpful, as one might have expected, for digitalis is ineffective in controlling ventricular tachycardia The patient was then given 0 3 Gm of quinidine sulphate by mouth, repeated for three doses at three hour intervals without any effect February 7, he was given 0 6 Gm of quinidine intravenously, whereupon the heart slowed from 151 to 120 in one minute The effect, however, was only temporary, the rate returning to 150 Further quinidine treatment was discontinued The heart beat remained rapid throughout, the patient gradually grew worse and died, February 10

There is very little doubt that the rapid rate here was due to paroxysmal ventricular tachycardia Had this diagnosis been made in time and had we known that under such circumstances extremely large doses of quinidine, such as 1 5 Gm at a time, might be necessary to restore the regular rhythm, the patient s life might have been saved, as illustrated by case 6

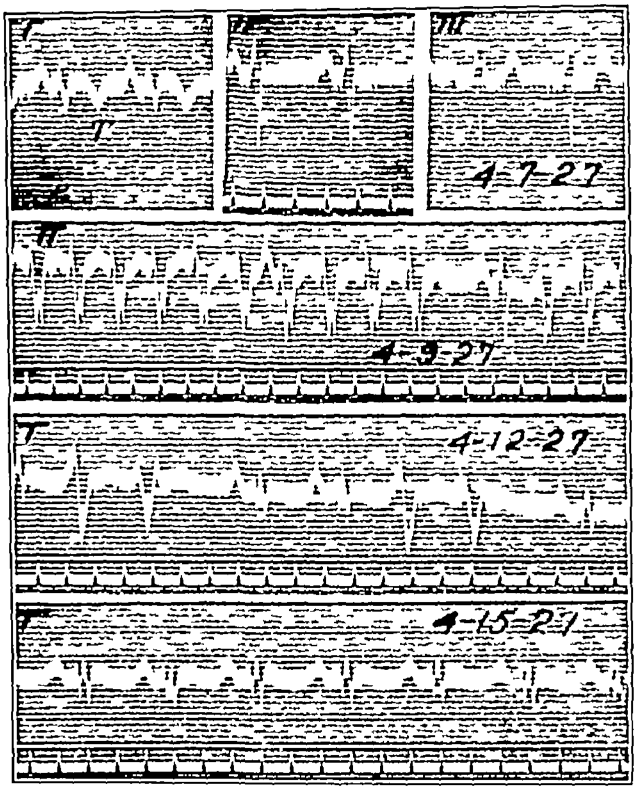

Fig 3 (case 6)—First set of tracings shows three leads taken two weeks after the onset of an attack of coronary thrombosis note sharply inverted dipped T_1 Second tracing shows rapid ventricular tachycardia interrupted with one normal beat Third tracing shows frequent abnormal ventricular beats indicating a partial effect of the quinidine on the irregularity seen in the second tracing Last tracing shows complete restoration of the normal rhythm on large doses of quinidine

Case 4—H L, a man, aged 56, seen at his home in consultation, March 3, 1927, had had sternal pain radiating to the left arm on effort for the previous two months Forty-eight hours before examination, while delivering an address, he was taken with a sudden pain in the upper part of the abdomen and the lower part of the chest radiating to the back His physician found him pulseless, could not hear any heart sounds and thought that he was dead Epinephrine, 1 3 cc was administered intramuscularly, and shortly afterward the pulse returned When the patient revived he complained of pain in the left arm

On examination he appeared to be in a moderate state of shock The blood pressure was 84 systolic and 50 diastolic The temperature was 97 8 orally and 101 rectally The heart was essentially normal The rate was 104 Numerous rales were present at both bases The urine contained a considerable amount of sugar Several days later a pericardial friction rub was heard and on another occasion partial heart block developed The patient gradually improved and began to do very well The pain and distress had all disappeared, the heart rate was around 90, and there was no glycosuria or evidence of congestion April 16, the heart rate was suddenly found to be rapid having risen to 171 The rhythm was regular with very slight changes in the length of the cycles at times The first heart sound varied in intensity the vagal pressure did not produce any slowing The pulse rate was 70 The blood pressure was 85 systolic and 70 diastolic There was Cheyne-Stokes breathing A diagnosis of paroxysmal ventricular tachycardia was made The patient was given increasing doses of quinidine sulphate by mouth beginning with 0.3 Gm and increasing to 0 5 Gm The following day on the latter dose the heart rate returned to 90 The drug was omitted and on the next day the rapid rate returned He was then given 0 5 Gm three times daily and the normal rhythm was reestablished This was continued for four days and then entirely omitted, as the patient was feeling fairly well April 26 after a period when no medication at all was being given and when the condition seemed very satisfactory so that he was expected to sit in a chair for the first time the patient suddenly died In this case the quinidine was effective in restoring the normal rhythm although some days later sudden death occurred which may have been due to rupture of the heart

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[16] Levine S A and Curtiss A N A Case of Ventricular Tachycardia and Auricular Fibrillation An Unusual Problem in Therapy Am Heart J 1 413 (April) 1926

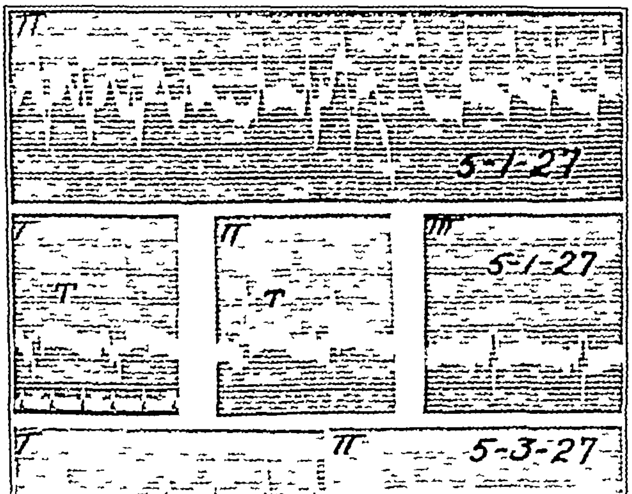

Fig 4 (case 7) —First tracing taken four days after onset of attack of coronary thrombosis shows auricular fibrillation with occasional extra ventricular systoles Second set of tracings shows normal rhythm the T waves in leads I and II have the characteristic high take-off Third set of tracings shows a paroxysm of ventricular tachycardia Last set of tracings shows return to normal rhythm following quinidine

CASE 5—S D L a man, aged 61 was seen at his home in consultation, Sept 1 1927 A few months before this attack he had had dyspnea on walking Three weeks before after a period of two strenuous weeks spent in cruising and yacht racing he had had a severe pain in the chest which lasted two days It felt like a ton of weight on the chest After this a pericardial friction developed with a temperature that ranged from 99 to 102 and lasted for two weeks In the past week Cheyne Stokes breathing was noted About three hours before the patient was seen he went into collapse and became agitated, violent and delirious The pulse rate was thought to be normal, but on careful auscultation the heart rate was found to be 204 The sounds were distant and the rhythm was regular with slight pauses The situation seemed fairly clear The patient had had an attack of coronary thrombosis beginning three weeks before and the present attack of collapse was due to the inception of paroxysmal ventricular tachycardia Six-tenths gram of quinidine sulphate in solution was forcibly poured down the patient s mouth and in about twenty minutes a most striking change in his condition occurred The heart rate was now 108 and all beats reached the wrist The active delirium terrific air hunger and dyspnea and the tremendous agitation all disappeared in a most dramatic way and the patient fell back in a peaceful sleep The heart rate remained about 100 and was perfectly regular after this The following day a sudden hemiplegia occurred, the patient became unconscious and died very peacefully, September 3 Here again quinidine had a most beneficial and specific effect in restoring the normal rhythm and improving the circulation Death was most likely due to the cerebral embolus following the dislodgment of a portion of the left ventricular mural thrombus This is a common accident in coronary thrombosis even when ventricular tachycardia does not occur

CASE 6—A. R a man, aged 53, three hours before he was seen in consultation at his home, March 24, 1927, was taken with a terrific attack of pain in the center of the chest radiating to both arms He vomited once The pain continued. On examination he was found to be in a cold perspiration The blood pressure was 158 systolic and 110 diastolic The heart sounds were very distant. There was a gallop rhythm, with a rate of 124 The diagnosis was obviously coronary thrombosis The patient had already had one-fourth grain (16 mg) of morphine hypodermically and another half grain (32 mg) was given directly before he was taken to the hospital During the first week in the hospital the course was the usual one of a severe coronary thrombosis He had almost continuous chest pain and difficulty in breathing The temperature ranged from 100 to 102 The blood pressure fell to 97 systolic and 74 diastolic The heart was regular with a rate of 100 (fig 3) April 7, the patient had an attack of transient auricular fibrillation, during which time there was considerable prostration. The following morning the heart was suddenly found to be very rapid with a rate of 198 The rhythm was essentially regular with slight detectable irregularities, and occasionally the intensity of the first heart sound changed A clinical diagnosis of ventricular tachycardia was made, which was confirmed by electrocardiograms (fig 3) The pulse was so feeble that no blood pressure could be obtained The condition seemed desperate. It was decided to inject 0 3 Gm of quinidine intravenously This however did not produce any effect and the tachycardia persisted. Increasing doses of quinidine were then given by mouth and when the dose of 1.2 Gm was reached a slight slowing of the heart beat occurred (fig 3) The patient was then given 1 5 Gm five times daily and the normal rhythm was established (fig 3) The drug was then omitted and the tachycardia returned The patient was therefore given 1 Gm four or five times a day for about five days Normal rhythm was reestablished and there was no return of the irregularity even after quinidine was omitted The improvement in the patient's general condition was striking and after a prolonged convalescence he recovered and became ambulatory This case illustrates quite decisively the specific effect of quinidine on ventricular tachycardia Here therapy seemed to be life-saving, as the patient was fortunate enough not to develop any of the other complications of coronary thrombosis[17]

CASE 7—T R K a man aged 55 for a year before the present attack had been treated for hypertension He had complained only of dyspnea on mild exertion April 27 1927, following slight exertion, he was suddenly taken with severe epigastric pain and weakness, and several hours later with dyspnea and a sense of constriction over the heart In the course of forty eight hours the systolic pressure fell from 220 to 148 The heart showed a questionable friction rub just outside the apex a gallop rhythm and a rate of 120 The temperature had risen to 101 There were moist rales at both bases On the evening of April 30, the heart rate was found to be 168 and totally irregular The blood pressure was 112 systolic and 84 diastolic The diagnosis was quite plainly coronary thrombosis, and an electrocardiogram (fig 4) showed the arrhythmia to be auricular fibrillation and paroxysmal ventricular tachycardia The patient was given 1 2 Gm of quinidine sulphate by mouth, divided in four doses, over a period of ten hours One half hour after the last dose the heart rate was found to be 126 and electrocardiograms showed a sinus rhythm with abnormal ventricular complexes (fig 4) Quinidine was discontinued after one more dose of 0 4 Gm, and the rhythm remained regular at the rate of from 120 to 130 throughout the day On the morning of the following day (May 3) it again rose rather gradually to 200 with an apparently regular rhythm Electrocardiograms at this time (fig 4) showed ventricular tachycardia The pulse was barely perceptible the rate being 130 The patient was given 0 4 Gm of quinidine by mouth, which was followed within an hour by a rapid and progressive fall in the rate to 124 all of the beats being felt at the wrist There had been a return of the normal mechanism (fig 4) During the course of the next two days he did not receive any quinidine, and there were short periods when the rate rose to 192 with a prompt return to 120 Oxygen was administered to relieve the cyanosis May 7, while the condition was apparently progressing favorably, the patient suddenly became very dyspneic and pulseless and died five minutes later Autopsy showed complete occlusion of the left coronary artery with a large infarct involving the tip of the left ventricle which had ruptured In this instance quinidine was effective in controlling the heart mechanism but the patient died of rupture of the heart

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[17] Levine S A and Stevens W B The Therapeutic Value of Quinidine in Coronary Thrombosis Complicated by Ventricular Tachycardia Am. Heart J 3 253 (Feb) 1928

Case 8—E L H, a man, aged 51, for three months before examination had noticed weakness and dyspnea on effort One week before admission to the hospital, Nov 7, 1927, he had had a 'quart of red fluid removed from the right side of the chest There was no history of an acute upset of chest pain or of palpitation On examination the patient did not appear to be in any distress The heart was moderately enlarged, with a rapid apparently regular rhythm, there were very faint heart sounds, and a to and fro friction rub was heard near the apex The blood pressure was 74 systolic and 60 diastolic There were rales at the bases of both lungs, with signs of fluid in the right pleural cavity The liver was enlarged and tender there was moderate pitting edema of both legs Electrocardiograms at this time (fig 5) showed a ventricular tachycardia with a rate of 153 The patient was given digitalis, on which he seemed to improve The heart mechanism, November 11 (fig 5) showed a sinus rhythm with defective intraventricular conduction During the first twelve days the heart rate varied between 100 and 150, and toward the end remained persistently at the rapid rate The blood pressure rose to 90 systolic and 65 diastolic November 16, the patient was found again to have a ventricular tachycardia (fig 5), the ventricular rate being 158 the auricular, 103 The heart sounds were faint and varied in intensity Digitalis was discontinued and two days later the patient was started on quinidine The first day he received 1 Gm in divided doses, the next day 0 8 Gm at noon and 1 Gm at 5 p m Within two hours after this last dose, the rate fell from 152 to 96 and he experienced a feeling of much easiness in the chest Quinidine was continued, the dose gradually being diminished to 0 3 Gm three times daily November 23 he again showed a rapid rate with electrocardiographic tracings revealing ventricular tachycardia During this time the blood pressure had risen to 105 systolic and 80 diastolic and the patient showed definite clinical improvement After a second dose of 0 8 Gm of quinidine the heart again became regular and remained so on a dose of 0 5 Gm four times a day Electrocardiograms November 27, showed a slow and regular sinus rhythm with defective intraventricular conduction (fig 5) The condition appeared to be progressing favorably and the patient felt better when on the afternoon of December 1, he complained of nausea and a peculiar sensation about the heart and within two minutes suddenly collapsed and died Autopsy revealed an old infarct on the posterior wall of the left ventricle 4 cm in diameter, with a small fresh infarction just above it There was occlusion of the circumflex branch of the left coronary artery This case illustrates the usual effective control of ventricular tachycardia by quinidine Here, one previous attack of tachycardia that had lasted several days ended, and recurred while digitalis was being taken

Case 9—C M a man aged 55, the evening before admission April 14 1928 shoveled about a half ton of coal without suffering any ill effect At 1 a m he was awakened by a violent constricting pain in the upper part of the abdomen and by a sense of something being 'stuck' in the throat He felt his heart going very fast and had difficulty in breathing At 5 a m he was admitted to the surgical service with a diagnosis of perforated peptic ulcer He refused operation, and when seen by one of us he was found to have a heart rate of 160 The heart sounds were feeble slightly irregular and of varying intensity, and there could be heard a definite to and fro friction The diagnosis was quite obviously coronary occlusion and the rapid rate was considered to be a ventricular tachycardia Unfortunately it was impossible to confirm this by electrocardiogram The patient was given 0 4 Gm of quinidine sulphate at 6 p m, and 0 6 Gm at 10 p m Sometime between 11 30 p m and 1 30 a m the heart rate fell from 140 to 92 He was put on a maintenance dose of 0.2 Gm of quinidine sulphate three times a day, but two days later he was again found to have a heart rate of 140 Within a few minutes after a dose of 0 6 Gm the rate fell abruptly to about 80 and remained slow and regular He continued taking 0 3 Gm of quinidine sulphate for five days with no return of the tachycardia The patient made an uneventful recovery and was discharged somewhat against our advice four weeks after admission in good condi-

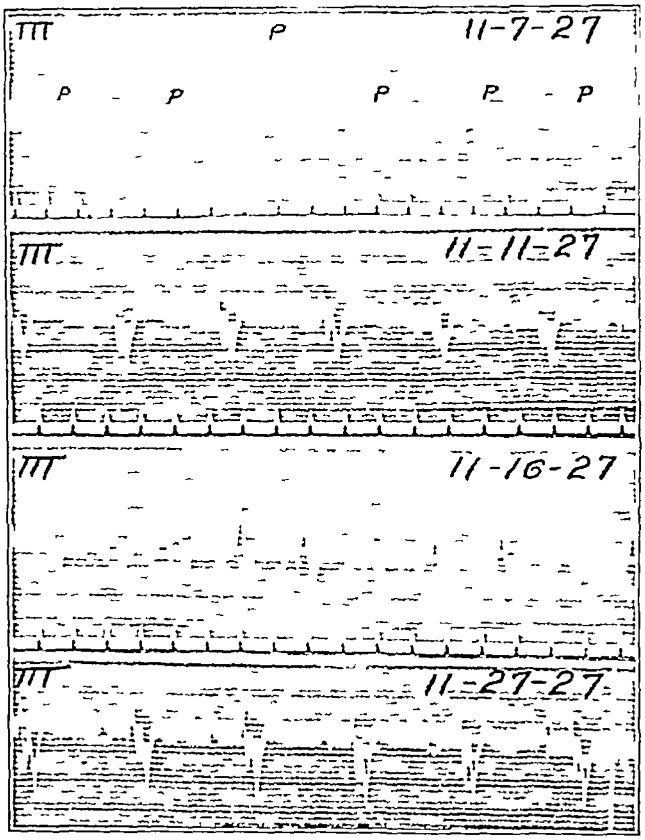

Fig 5 (case 8)—First tracing shows ventricular tachycardia with independent auricular rhythm, ventricular rate 153 auricular rate 114 Second tracing shows normal rhythm Third tracing shows return of ventricular tachycardia which was persisting for days Last tracing shows return of normal rhythm as result of quinidine tion. Though the arrhythmia was not proved by electrocardiogram to be ventricular tachycardia, its occurrence in an obvious case of coronary thrombosis, the characteristic varying intensity of the heart sounds and the slight irregularity, and its prompt cessation with quinidine leave little doubt as to the diagnosis. This illustrates the favorable effect of quinidine on ventricular tachycardia in a patient with coronary thrombosis who made a most satisfactory recovery.

Case 10.—M. F., a woman, aged 50, who had previously been very well, nine days before admission had a sudden attack of precordial and epigastric distress associated with vomiting and some shortness of breath. Vomiting had continued. The patient complained that her heart was "throbbing" but she had not had any real pain. Physical examination showed moderate cardiac enlargement, a rate of 180, and heart sounds of varying intensity. There were a few crepitant rales at the bases of the lungs, slight edema of the ankles was noted, and the blood pressure was 110 systolic and 80 diastolic. Electrocardiograms showed a ventricular tachycardia with complete dissociation of auricular and ventricular complexes. Vagus and ocular pressure did not have any effect on the cardiac rate. The patient was started on 0.3 Gm. of quinidine sulphate and the dose was increased by 0.1 Gm. at four hour intervals throughout the day, until she was receiving 0.8 Gm. Electrocardiograms taken the day after admission showed a ventricular rate of 200 and an auricular rate of 100. The patient failed rapidly and died two days after admission. Autopsy was not permitted. In this case quinidine sulphate in doses up to 0.8 Gm. failed to produce any slowing of the heart; in fact, there was a slight acceleration.

SUMMARY

1. Clinical experience in ten cases showing ventricular tachycardia indicates that quinidine sulphate has in most instances a specific effect in restoring a normal rhythm.

2. Ventricular tachycardia occurs occasionally in patients who have no organic heart disease but more commonly in those with coronary thrombosis. Although quinidine does not have any effect on the other complications of coronary thrombosis, such as rupture of the heart or production of emboli, its beneficial influence on ventricular tachycardia is most dramatic and may be life saving.

3. It is highly probable that ventricular tachycardia is of the nature of a circus movement like that of auricular flutter and auricular fibrillation, and that the effect of quinidine is similar in all these conditions.

270 Commonwealth Avenue.

Contributors to Medical Science.—In the field of medical and vital statistics two remarkable men, John Graunt (1662) in his famous "Bills of Mortality" and William Farr (1839-1880) in his collected studies in "Vital Statistics" (1885) outlined the principles and indicated the methods on which modern public health bookkeeping is based. In two other branches of preventive medicine most substantial advances were made—tropical medicine and mental hygiene. In the former, Laveran, in 1880, by his discovery of the causative agent of malaria, and Sir Ronald Ross, in 1897, in establishing the mode or transmission of the disease made possible the elaboration of procedures for its control. In 1901 the Commission on Yellow Fever of the Medical Corps of the United States Army, consisting of Reed, Carroll, Lazear and Agramonte, by heroic and self-sacrificing experiments elucidated the fact that yellow fever is also an insect borne disease. Other outstanding contributors in this field are Sir Patrick Manson, who in 1879 first proved that insects serve as the vectors of parasites which cause human disease, Sir David Bruce, Leishman and Fritz Schaudinn, who also discovered the spirochete of syphilis. These are but a few of the contributors to medical science whose work has made life in the tropics possible for the white man.—Fitzgerald, J. G.: Some Aspects of Preventive Medicine, *Canad. M. A. J.*, February, 1929.

INTESTINAL PARASITISM SIMULATING APPENDICITIS *

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PHILADELPHIA

Intestinal parasitism is commonly manifested by a collective group of symptoms and pathologic lesions of such a varied degree of intensity that the recognition of these disorders is often rather uncertain. Parasitic diseases, with few exceptions, have an indefinite period of incubation, their course commonly is protracted over a long period and they have, as a rule, an uncertain termination. Such is amebic dysentery, which commonly is manifested by the acute symptoms of frequent defecation, tenesmus, and mucous or bloody discharges. Not infrequently these acute symptoms may not appear until some time later in the course of the disease, or may be entirely wanting when the disturbance is mild in character. Nevertheless, the disease follows its normal course of ulceration of the mucosa of the colon, to be manifested later in the form of a diffuse and rather indefinite form of colitis.

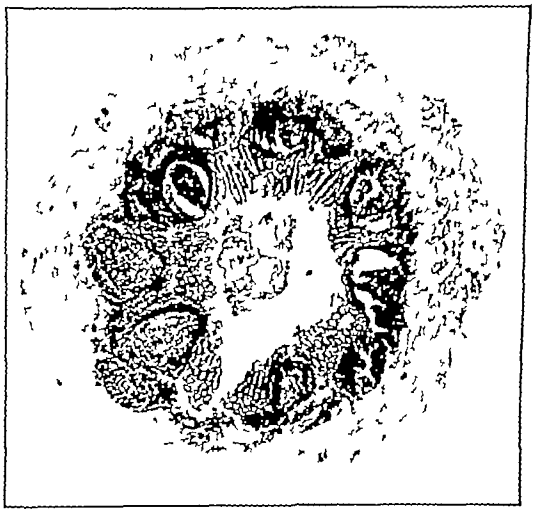

Fig. 1.—Section of Oxyuris vermicularis in lumen of the appendix.

Certain parasites, such as *Oxyuris vermicularis*, which commonly inhabits the appendix and the large intestine, may give rise to rather obscure symptoms in these regions and the same is true of *Trichuris* (*Trichocephalus*), or whipworm, which inhabits the cecum and may cause a chronic, indefinite form of catarrhal typhlitis and appendicitis.

Infestation with *Ascaris lumbricoides*, affecting especially children, does not manifest any definite symptoms on which one may base a certain diagnosis. This can easily be made, however, by the finding of the eggs in the feces. This parasite has more or less a wandering habit through the whole extent of the small intestine, and its presence in the lower part of the ileum and eventually in the cecum or appendix may be manifested by symptoms more or less localized in the appendicular region, resembling appendicitis.

A rather interesting phase in the symptomatology of intestinal parasitism is illustrated by schistosomiasis, a disease caused by *Schistosoma mansoni*, *S. japonicum* and *S haematobium*. These are blood parasites found in the inferior vena cava, the mesenteric vein, and the hemorrhoidal plexuses of the rectum and the bladder, respectively. Since the eggs of these parasites are discharged into the blood stream, they may be carried to any part of the body, including, of course, the appendicular region.

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* Read before the American Society of Tropical Medicine, Washington, D. C., May 1, 1928.

* From the Division of Medical Zoology and Tropical Medicine, Department of Pathology, University of Pennsylvania School of Medicine.

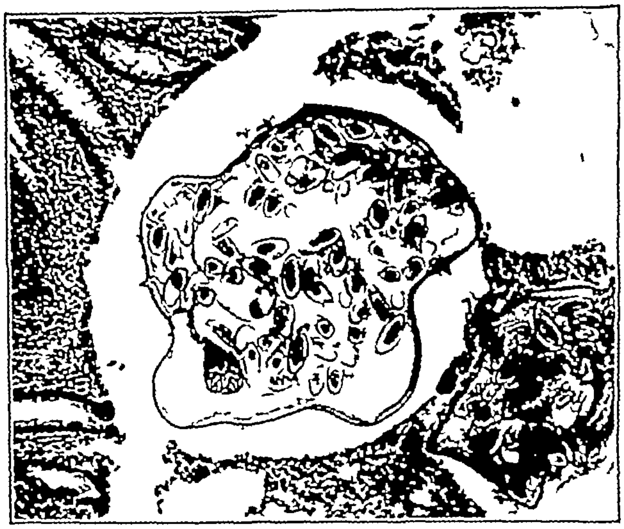

Fig 2.—Eggs of Oxyuris vermicularis in section of the parasite in appendix (high power)

Figure 6 shows the lodgment of *Schistosoma* eggs in the mesenteric lymph nodes of the pelvis and the pelvic portion of the ureters, as well as in the blood vessels of the cecum and appendix. The lodgment of the eggs in these localities, as is readily understood, may be the source of mechanical irritation giving rise to symptoms simulating in all respects chronic appendicitis, more especially if the eggs happen to be lodged in the region of the appendix.

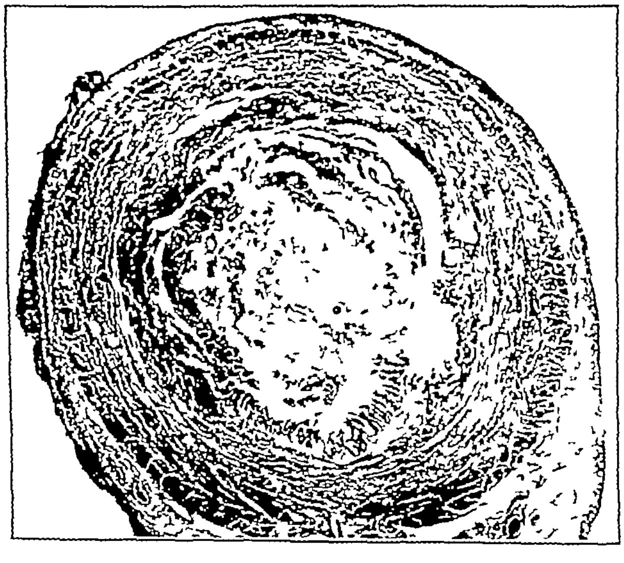

Fig 3.—Ulceration of mucosa in amebiasis of the appendix (low power)

Acute appendicitis, as classically understood, is an acute bacterial infection which calls for immediate operation in order to avoid its fatal spread to adjacent structures. Besides this, however, there are the subacute and chronic types of appendicitis in which immediate operation is not only unnecessary but often undesirable and certainly should never be performed before a more careful study of the situation has been made.

Subacute or chronic appendicitis may result from various causative factors, among which parasitic infestation of this organ is rather more common than is generally conceded. It should be added here that parasitic infestation of this organ is usually, if not always, a secondary manifestation, because infestation of the cecum and other portions of the large intestine or the lower portion of the small intestine is in nearly every case the primary seat of the infection.

To go into a lengthy discussion of the secondary manifestations of intestinal parasitism would be out of place here. Suffice it to say that extensive ulceration of the large intestine, either in part or in toto in amebic dysentery, is of common occurrence. Appendectomy, common and fashionable as it may be, is nevertheless a serious operation the performance of which, unless absolutely necessary, is certainly to be avoided, and to perform this operation, except under dire necessity, in cases of ulceration of the cecum or colon, is, to my mind, inexcusable. It is needless to point out that in such cases the formation of adhesions is greatly favored, to say nothing of the possibility of the operative procedures inducing a fatal peritonitis.

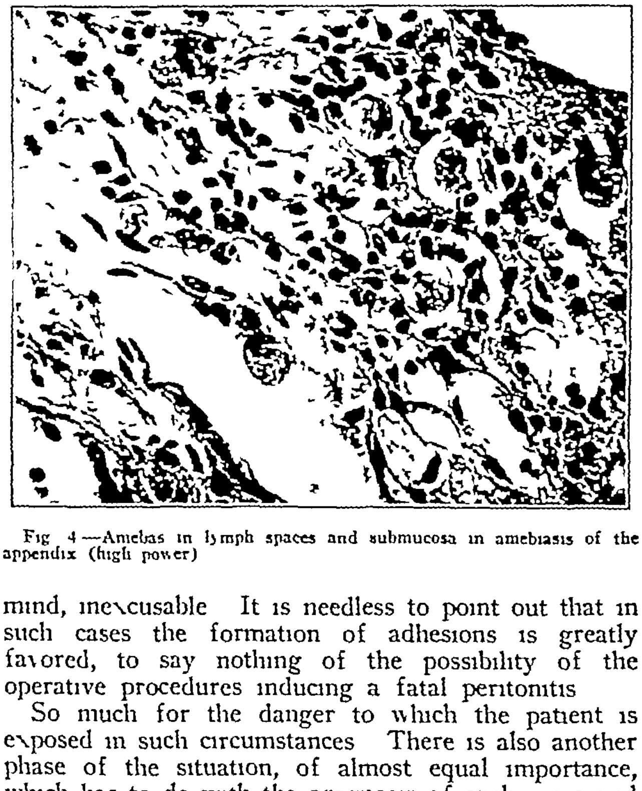

Fig 4.—Amebas in lymph spaces and submucosa in amebiasis of the appendix (high power)

So much for the danger to which the patient is exposed in such circumstances. There is also another phase of the situation, of almost equal importance, which has to do with the prognosis of such cases and indirectly with the reputation of the surgeon. It can be appreciated that the removal of the appendix in cases of intestinal parasitism is never a cure and only in rare cases does it alleviate any of the symptoms. It is for this reason that conscientious prognosis can be based only on a more careful diagnosis.

If care is taken in the preoperative examination, an operation may be avoided, or, in case it is found necessary, the patient should be given to understand that while he has appendicitis he also has intestinal parasitism, and although an operation is advisable in order to avoid possible immediate complications, it will not necessarily rid him of the symptoms. In this way a great deal of unpleasantness to the patient the surgeon and every one concerned can easily be avoided.

In acute appendicitis there may not, of course, be any choice and operation is the logical procedure, but in subacute or chronic cases there are a few salient points to be remembered Diarrheas or other manifestations common to intestinal parasitism absence of fever, mild leukocytosis and indefinite localization of pain should put the surgeon on the lookout for intestinal parasites, and while careful clinical and laboratory study is advisable in all cases, it should be more especially considered when such symptoms are noticed

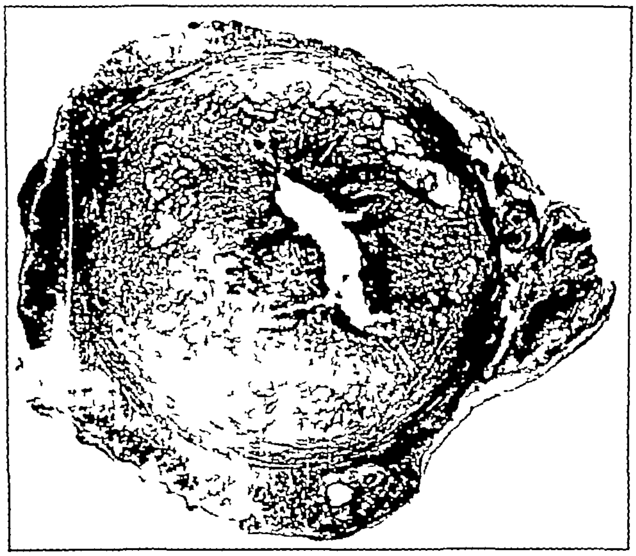

Fig 5—Clusters of eggs of Schistosoma haematobium in schistosomiasis of the appendix

The preoperative procedure in all subacute or chronic cases of appendicitis should include

1 Examination of the feces for intestinal parasites, whether in the vegetative or encysted form of protozoa, or as the eggs, larva or adult forms of metazoa

2 Proctoscopic examination of the colon for ulceration

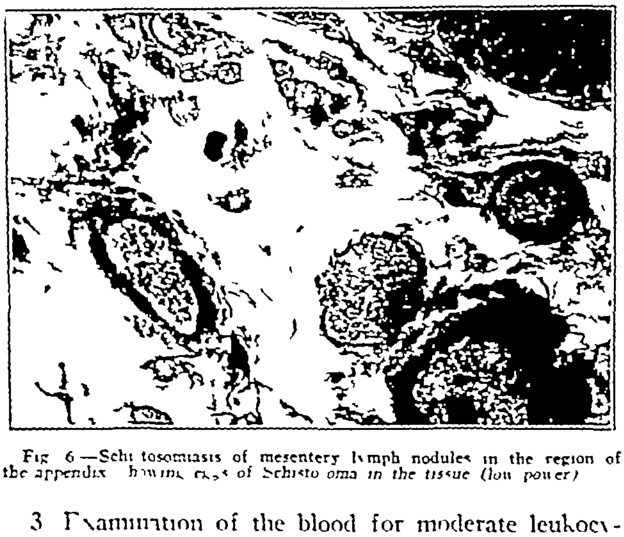

Fig 6—Schistosomiasis of mesentery lymph nodules in the region of the appendix *showing eggs of Schistosoma in the tissue (low power)*

3 Examination of the blood for moderate leukocytosis and eosinophilia for it must be remembered that in cases of parasitism as well as in the ordinary appendicitis a mild leukocytosis independent of the appendical condition is often observed the blood picture is not very reliable but it is useful nevertheless Of especial interest in this connection is the presence of eosinophilia, which with few exceptions is to be found in the infestation of the intestine with metazoan parasites

Should the diagnosis of intestinal parasitism be made, the removal of these parasites and the appropriate treatment of the disorder should receive consideration before an operation for appendicitis is performed

It might be objected that there is not sufficient time for such procedures when a few hours may mean life or death, but it should be remembered that I am not referring to the acute bacterial appendicitis, which is easily recognizable and distinguishable from the subacute and chronic types for which these precautions are especially recommended It should also be noted that the carrying out of these examinations can be made in one, or at the most two, hours, in a well equipped hospital

In elucidation of the parasitic disorder of the intestine which may simulate appendicitis, the finding of *Oxyuris vermicularis* in the appendix may be mentioned In our general routine pathologic examination of this organ after appendectomy, experience shows that this parasite, as well as *Trichocephalus* and the eggs of *Schistosoma,* in this organ or its vicinity have often been encountered An amebic disease of the cecum may clinically simulate appendicitis, but, as is well known, the ameba rarely invades the appendix Clinical interpretation of this fact may be further illustrated by a brief summary of the following cases from the literature

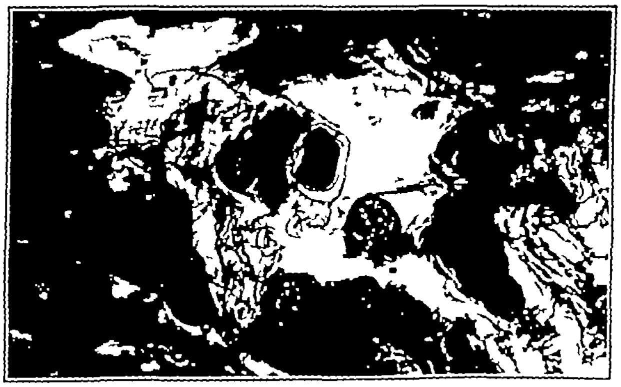

Fig 7—*Same as figure 6 (high power) showing the egg of Schistosoma in the tissue*

Gonzales,[1] citing several erroneous diagnoses due to a lack of the examination of the feces, says

> In one of these cases an eminent surgeon performed a laparotomy for the purpose of removing the appendix and on finding the appendix perfectly healthy, decided to remove the right ovary which was condemned by default as being responsible for the pain from which the patient suffered
>
> In another case three internists and two surgeons diagnosed appendicitis and an operation was fixed for the next day In the evening however, the diagnosis of intestinal parasitism made by another physician stopped the operation and it is now seven years since that appendix has been awaiting the execution of that operative sentence
>
> *In two other cases surgical intervention was decided on* as in the others but an opportune coprological examination commuted the sentence to the evacuation of the worms that simulated appendicitis

Sir Leonard Rogers[2] mentions the close resemblance of amebic disease of the intestine to appendicitis, pointing out that it may lead to a useless and dangerous operative procedure

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[1] Gonzales R The Differential Diagnosis of Appendicitis and Bilharziasis

[2] Rogers Leonard Recent Advances in Tropical Medicine

Cope,[3] as a result of his extensive experience in Mesopotamia, found that operative procedures in these cases are rarely required, and may even lead to conditions of shock induced by operation, removing the last chances of the patient's recovery

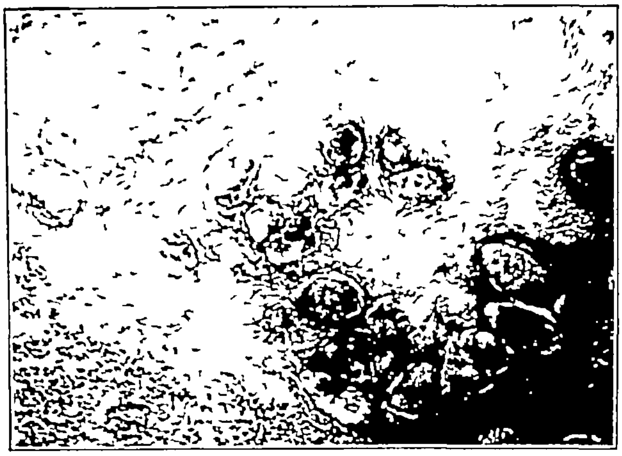

Fig 8 —Chronic type of inflammation and eggs of Schistosoma in schistosomiasis of the bladder

Sir Leonard Rogers, in commenting on this, makes the following statement

> Many surgeons, however, appear to be ignorant of this, if the writer can judge by the considerable proportion of chronic dysentery patients invalided home from India who are found by the Indian Office Medical Board to have their appendixes removed without lasting benefit This is due to the frequency of slight thickening of the cecum in chronic or latent amebic disease being mistaken for a thickening of the appendix
> Even death after such operations has been recorded by P A Petridis recently

In my experience, it has been rather striking to note that, of all the cases of intestinal parasitism coming under observation, the history reveals a previous operation of appendicitis in about 39 per cent, with no lasting improvement from the operation

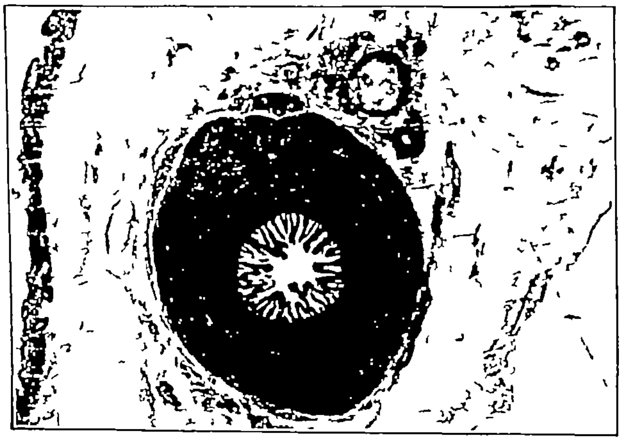

Fig 9 —Schistosomiasis of the ureter near the appendix showing egg of Schistosoma in the surrounding tissue

This brief discussion of the relation existing between intestinal parasitism and appendicitis clearly points to the advisability, except, perhaps, in acute appendicitis, of making a study, as complete as possible, of the true etiologic factors responsible for the pathologic condition of this organ and the presenting symptoms before an operative procedure is decided on This is becoming of increasing importance if it is taken into consideration that statistical reports by several investigators in the United States show 10 per cent, and as high as 50 per cent, of parasitic infestation of the intestine in temperate and northern climates, brought about by the dissemination of parasitic diseases through the recent ingress of peoples from the tropical and oriental countries to these latitudes

Fortunately, the diagnosis of these disorders is so simplified by a careful proctologic and coprologic examination and the search for easily recognized protozoan and metazoan parasites that there is no more reason for neglecting these important procedures in the study of a case than there is for neglecting the Wassermann reaction, the blood count, analysis of the urine, and other routine procedures

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[3] Cope V Z Lancet 1 579 (March 13) 1920

FELONS ACUTE LYMPHANGITIS AND TENDON SHEATH INFECTIONS

DIFFERENTIAL DIAGNOSIS AND TREATMENT *

SUMNER L KOCH, M D
CHICAGO

Although the essential points in the differential diagnosis of acute infections of the hand were clearly set forth by Kanavel[1] some years ago, the number of cases which have come to my attention in the past six months in which there was a failure to make an exact diagnosis, and the fact that a number of such cases have occurred in medical men leads me to believe that the subject deserves reemphasis in the clearest possible terms

The characteristic symptoms of a felon are throbbing pain, swelling and tenderness which are limited to the distal phalanx There may be a history of a penetrating wound from a sliver, a pin or a sharp pointed instrument, and there may be a tiny scar or evidence of recent injury Not infrequently the etiologic factor has been unnoticed The symptoms develop rapidly—within twenty-four or forty-eight hours, they are progressive and severe Frequently the patient has spent hours walking the floor with pain before seeking relief On examination one finds redness, swelling and almost boardlike induration, which is due in part to the firm consistency of the thick palmar skin There is no fluctuation because of the great tension, and the slightest attempt to elicit it causes intense pain The swelling does not extend above the distal phalanx nor are there red streaks running up the arm Movement of the finger does not cause exaggeration of the pain There is no lymphadenopathy at the elbow or axilla, and rarely is there fever of more than 1 5 degrees

With such a clinical picture there can be no doubt as to the presence of pus in the anterior closed chamber of the distal phalanx To wait for fluctuation or for the infection to "come to a head" is to cause the patient intense and unnecessary suffering The finger should

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* From the Department of Surgery Northwestern University Medical School

* Part of a paper read before the Muscatine County Medical Society Muscatine Iowa Sept 11 1928

[1] Kanavel A B Infections of the Hand Philadelphia Lea & Febiger 1911

be opened at the earliest possible moment under a general anesthetic, such as nitrous oxide or ethylene To freeze such an infected area causes further injury of the tissues, and to infiltrate it with procaine may diffuse the infection still more widely Neither method, moreover, gives satisfactory anesthesia because the pus under tension has rendered the sensitive finger tip abnormally hyperesthetic If nitrous oxide or ethylene is not available, the digital nerves at the base of the finger should be blocked with procaine

To drain such an infection, an incision at one side of the finger suffices if it is long enough and if the knife is made to sweep across the palmar surface so as to divide the fibrous septums that pass vertically from the skin to the periosteum (fig 1) The incision (fig 2) should not extend upward far enough to permit invasion of the sheath of the deep flexor tendon at its insertion on the base of the distal phalanx The horseshoe shaped incision so frequently advised is unduly long in healing, and leaves a painful scar over the finger tip and an anesthetic area distal to the scar which is particularly annoying to any one attempting to perform delicate manipulations

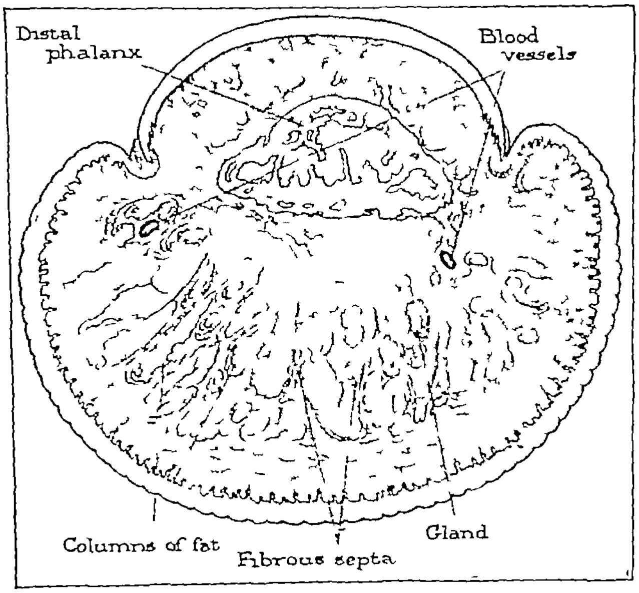

Fig 1 —Cross section of the distal phalanx of the finger (After Kanavel)

If the condition is recognized early there should not be any necessity for curetting or excision of the bone Because the digital arteries are compressed by the pressure of the exudate as they pass through the closed space and because there is a direct path through the columns of fat for the transmission of infection from subcutaneous tissue to periosteum bone involvement does take place early, but it should not occur if the symptoms are correctly interpreted and the condition properly treated early in the course of the infection

After the incision is made one should pack a little wedge of petrolatum gauze into the drainage wound in such a way as to hold the wound edges apart without preventing the escape of pus Otherwise one may be disappointed to find the wound surfaces agglutinated at the end of twenty-four hours and drainage completely blocked The finger is kept enveloped in a hot wet dressing until the infection is under control

ACUTE LYMPHANGITIS

An acute lymphangitis usually results, just as does a felon, from an apparently trivial injury—a scratch, a pin prick, an injury from a sliver, a surgical needle or tonsil snare—or the abrasion of a superficial healing wound Within a few hours local symptoms appear —discomfort, pain, redness and swelling General symptoms—malaise, restlessness, rise of temperature—appear soon after, in the more severe cases there is a chill, high fever and prostration Within the first twelve hours, sometimes even concomitant with the first symptoms, red streaks running up the forearm make their appearance and within twenty-four hours the lymph glands at the elbow or axilla or both become enlarged and painful

Aside from the immediate site of the primary injury there are no definitely localized symptoms The entire finger affected is reddened and swollen Characteristically the swelling and lymphangitis are more pronounced on the dorsum of the finger and hand, for the lymphatics "take the shortest course to the back of the hand "[2] The distal phalanx is no more tender than any other part of the finger except just at the site of injury Movement of the finger does not intensify the pain, and it can be passively extended and flexed without undue pain With such a clinical picture there should not be any doubt as to the diagnosis of an acute lymphangitis

The treatment indicated is rest in bed, the application of a hot wet dressing from the finger tips to the axilla, and abstinence from any form of active surgical treatment To cut into such a finger in the first few days or even weeks, before definite localization of the infectious process has occurred, is to court almost certain disaster It is scarcely necessary to cite specific instances One tragic case was reported recently[3] Within the past year I have seen three similar cases, all in members of the medical or dental profession One recovered without serious mishap except a severe exaggeration of all the acute symptoms and a somewhat prolonged convalescence, in another the infection, which primarily was in the superficial tissues of the distal phalanx, was carried into the tendon sheath of the thumb, and went on to a severe suppurative infection of the radial and ulnar bursae, in the third the infection went on to a rapid and fatal termination

In such cases if conservative measures—absolute rest in bed, forced administration of fluids, and the constant application of hot wet dressings to the entire upper extremity[4]—do not bring about an arrest of the infectious process, one may be certain that surgical intervention will only hasten the inevitable and fatal outcome

TENDON SHEATH INFECTIONS

In unusual cases, tendon sheath infections are metastatic in origin, as a rule they result from direct inoculation through a penetrating wound, less often they develop secondarily to a more superficial infection The characteristic symptoms are pain and swelling of the entire finger, with swelling more pronounced on the dorsum of the finger, and tenderness over the anatomic position of the tendon sheath The patient holds his finger in a semiflexed position, and any attempt to extend it causes him to wince with pain The only exception to this rule is in those cases in which the tendon sheath has been opened so widely by the original injury as to permit free drainage, and in which the diagnosis should be obvious So characteristic are these symptoms—the tenderness which permits one to map out the extent of the tendon sheath, the position in which the finger is held and the excruciating pain, invariably manifesting itself by a quick contortion of the face at any attempt of the examiner to straighten the finger—that there should never be any questions as to the diagnosis of a tendon sheath infection within twenty-four or forty-eight hours after its onset

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[2] Kanavel A. B Infections of the Hand ed. 5 Philadelphia Lea & Febiger 1925 p 295

[3] Koch S L. J Indiana M A **21** 137 (April) 1928

[4] To keep a big moist dressing hot, a powerful light suspended close above the dressing serves satisfactorily Such a device keeps the wet dressings at an even temperature and avoids the necessity of changing them at frequent intervals a procedure that is disturbing and painful for the patient and wasteful of surgical supplies

The only condition that can cause such exquisite pain on any attempt to straighten the finger is an acute suppurative arthritis of one of the interphalangeal joints—a comparatively rare condition In such a case the limitation of the signs of inflammation to the area about the joint, and the absence of tenderness over the tendon sheath, should make the diagnosis clear

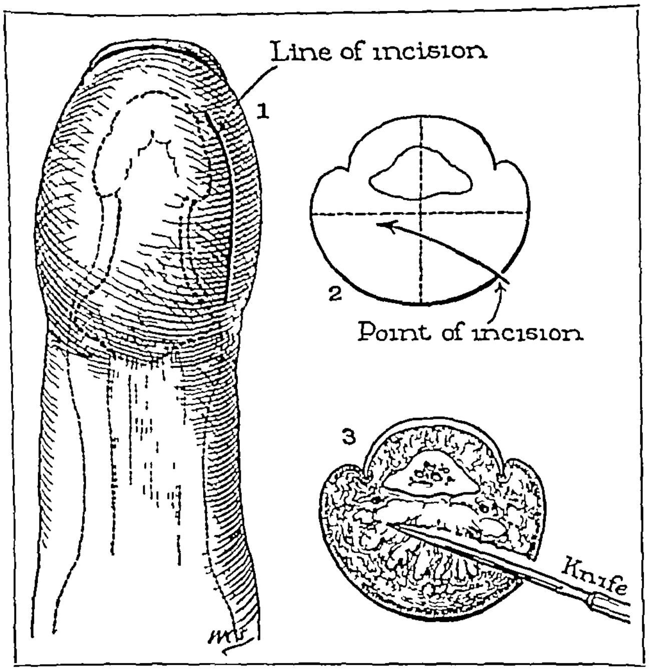

Fig 2—Proper incision for drainage of a felon.

One must remember that, in neglected infections of the tendon sheaths of the thumb and little finger, the pressure of the exudate rupturing from the radial and ulnar bursae at the wrist compresses the median and ulnar nerves and gradually obtunds sensation and pain, but in such cases the early symptoms, the history of gradual decrease of pain concomitant with increasing numbness of the fingers, the increasing swelling and inflammation of the forearm and the general symptoms of an acute infectious process should not leave one in doubt as to the exact nature of the condition present

The correct methods for draining an infection of the tendon sheaths, the importance of avoiding secondary and mixed infections if the tendon is to be saved, of not permitting the hand to become edematous and macerated by the prolonged use of hot wet dressings, of maintaining the hand in the "position of function" and of bringing about early mobilization have been stressed elsewhere[5] The most careful operative and postoperative attention, however, cannot produce satisfactory results unless the correct diagnosis is made early in the course of the infection

SUMMARY

The differential diagnosis of a felon, an acute lymphangitis and a tendon sheath infection depends on definite symptoms and signs which can be readily recognized if they are kept in mind and sought for To make such a diagnosis is of the utmost importance, for the avoidance of bone destruction in the case of a felon and of tendon necrosis in the case of a tendon sheath infection depends on early incision and drainage In the treatment of an acute lymphangitis, on the other hand, abstinence from surgical treatment is imperative if one is to avoid the possibility of converting a local infection into a general septicemia

54 East Erie Street

THE TREATMENT OF BURNS WITH NORMAL HORSE SERUM

REPORT OF CASES *

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In the management of burns, it has been stated that the best treatment is that which fulfils a threefold purpose (1) It must favor separation of the slough, (2) it should maintain sterility of the resulting wound, and (3) it must promote granulation and the formation of new epidermis To these requirements we would add a fourth, namely, that the treatment should prevent the absorption of toxins from the burned area in order to combat what is variously termed "constitutional reaction," "toxemia," or ' secondary toxic wound-shock "

The importance of preventing toxemia has been pointed out by Gordon,[1] who says that "if a sound and simple means of preventing the toxemia which follows the burn could be found, a great step in the right direction would have been taken and a happier outlook could be entertained" Lee[2] has emphasized the fact that the problem of secondary toxic wound-shock has for many years been unsolved because of lack of knowledge of the cause However, during the last few years experimental work conducted by several research workers has demonstrated that the constitutional reaction following the burn is due to absorption of toxins from the burned tissue, and this fact is now generally recognized We shall endeavor to point out a simple method of controlling the toxemia

The various methods of treatment advocated for burns are so numerous that we have been reluctant to report our own method However, the treatment here described does not merely embody the use of another remedy, rather, it is a method based on sound physiologic principles, the application of which yields results not obtainable by other methods

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[5] Koch S L Prevention of Contractures Following Infection of Hand J A M A 88 1214 (April 16) 1927

* Read before the Seventh Annual Convention of the National Association of Police and Fire Surgeons and Medical Directors of Civil Service Commissions of the United States Atlantic City N J Oct 4 1928

[1] Gordon R M Lancet 1 336 (Feb 18) 1928

[2] Lee W E S Clin North America 8 901 (Aug) 1928

Our attention was directed to a report by Robinson[3] entitled "Artificial Cell Proliferation with Horse Serum in the Treatment of Burns," which appeared in 1917 He had achieved success in inducing growth of cellular tissue in cases of atrophy due to imperfect nutrition and, believing in the possibility of promoting through analogous processes the repair of tissues destroyed by burns, he made a practical application of the idea

Robinson's patient, a woman, aged 45, was severely scalded with boiling water The injured surfaces were the upper and middle third of the right leg, from 10 to 12 inches in length and from 4 to 8 inches wide, the calves of both legs the left ankle, both buttocks, the left thigh, and the right cheek The surface area of devitalized skin exceeded one third of the entire surface of the body The burns were about equally of first and second degree in extent. On account of the extensive loss of skin, it was impossible to bring about satisfactory results through skin grafting The burns were dressed with antiseptic ointment until the tenth day, when Robinson decided to use normal horse serum containing a small percentage of cresol The serum was sprayed on the marginal skin cells and the parts were then covered with rubber tissue The dressings were removed and the serum reapplied several times each day Complete recovery ensued after ten days of this serum treatment and the patient was discharged from the hospital twenty-one days after admission

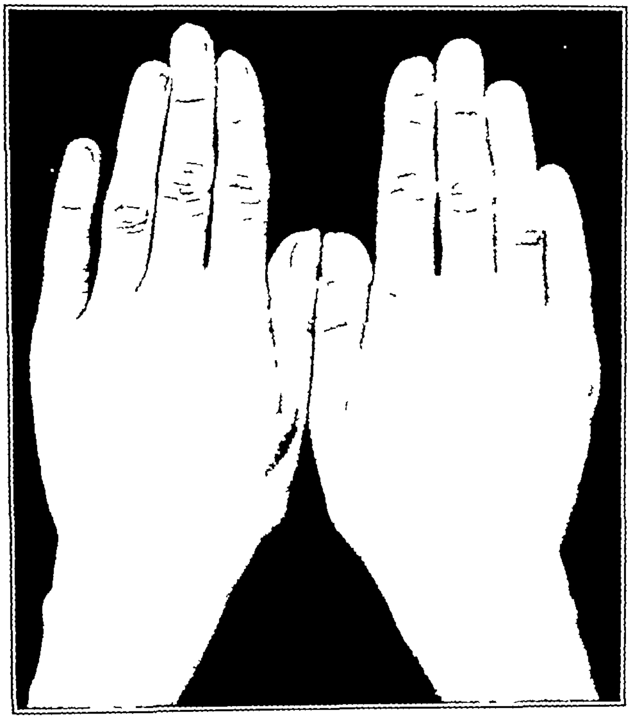

Fig 1 (case 1) —The skin on the injured right hand shows a greater number of wrinkles than does the skin of the left hand when the fingers are extended Otherwise the right hand appears normal like the left

Our first opportunity to use normal horse serum in the treatment of burns came late in 1920

REPORT OF CASES

CASE 1 —F C., a young woman received a second degree burn of the entire back of the right hand and proximal phalanges of the thumb and fingers from ether which had become ignited. The burn had been dressed with antiseptic ointment for a week by another physician The patient came under our care on the eighth day The burned area at that time was covered with a thick crust under which was an accumulation of pus and blood We removed the crust and placed the hand for an hour in a bath of warm physiologic solution of sodium chloride Several pieces of devitalized tissue were then removed with forceps and scissors, after which the entire burned area was thoroughly sprayed with normal horse serum from an ordinary oil atomizer The wound was then covered with rubber tissue held in place by a light gauze bandage During the next five days, the normal horse serum was applied twice daily and then once daily for four days, when the entire burned area was found to be completely covered with healthy epidermal tissue, and there was an entire absence of cicatricial tissue This new tissue was a deep pink, and for several months it was quite sensitive to heat and cold as well as to pressure However, the color bleached out in the course of a year and, today, it is quite difficult to detect which hand was injured In figure 1, showing the hands with the fingers extended, the skin on the injured right hand shows a greater number of wrinkles than does the left But in figure 2, showing the hands with the fingers tightly flexed, the character of the skin on the two hands is practically the same This patient has the full, normal use of the right hand and there are no contractures

The surprisingly satisfactory result in this case encouraged us to use the method at every opportunity in the future, and, during the past eight years, we have employed it in the treatment of several burns of relatively small area The following brief case reports will serve as examples of the effectiveness of this method of treatment

CASE 2 —C N., a woman, had a boil on the extensor surface of the left forearm near the elbow She had applied a wet dressing of a solution contained in a bottle labeled laudanum" This bottle, however, had been in the house for several years and apparently had been refilled with some acid solution There was a first degree burn of the entire surface covered by the dressing, comprising an area of 3½ by 4 inches on the extensor surface and about 2½ by 4 inches on the flexor surface of the forearm Antiseptic ointment was applied as a temporary dressing, and the next day this was removed and the forearm placed in a bath of warm physiologic solution of sodium chloride Then the burned areas were sprayed with normal horse serum and covered with rubber tissue and lightly bandaged The dressings were changed once daily and on the fifth day the wounds had entirely healed and were covered with healthy skin

CASE 3 —F H, a truck driver, carried a pail of water to the front of the truck with the intention of filling the radiator in which the water was boiling While he was in the act of loosening the radiator cap, the steam pressure forced the cap up and live steam enveloped the patient s face and right forearm causing second degree burns Antiseptic ointment was applied to the face, and the forearm was placed in a bath of warm salt solution and then sprayed with normal horse serum and covered with rubber tissue held in place by a bandage Five hours later, the patient returned complaining of pain in the face but said that the forearm was comfortable except for an area about 1 inch square near the base of thumb where the dressing had worked loose The patient was transferred to the Nyack Hospital, where the forearm was again treated with normal horse serum

The ointment was removed from the face and the entire face was sprayed with normal horse serum A face mask of rubber tissue was then applied and held in place by bandages The dressings were changed and normal horse serum was reapplied every four hours After two days the face was completely healed and was left exposed to the air The patient was discharged from the hospital on the sixth day and returned to work on the seventh day The burned areas were covered with healthy epidermal tissue There was no infection and no suggestion of any scar tissue The patient stated that the normal horse serum dressings were very soothing and comfortable.

CASE 4 —H G a laboratory assistant while removing with a pipet some pure phenol from a bottle spilled some of the acid on the flexor surface of the right arm near the bend of the elbow The acid was washed off with alcohol and antiseptic ointment applied We saw the patient on the day following the injury. There was a second degree burn of the forearm approximately 3 by 5 inches in area. The ointment was removed and the forearm placed for one half hour in a bath of warm saline solution. Devitalized tissue was removed with forceps and scissors from practically the entire burned area, which was then thoroughly sprayed with normal horse serum from an atomizer. The wound was covered with rubber tissue and lightly bandaged. This entire treatment was repeated twice daily for four days. On the fifth day, the wound was completely healed and covered with healthy, epidermal tissue of a deep pink color. There was entire absence of scar tissue.

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[3] Robinson E. P Ann Surg 65 367 (March) 1917

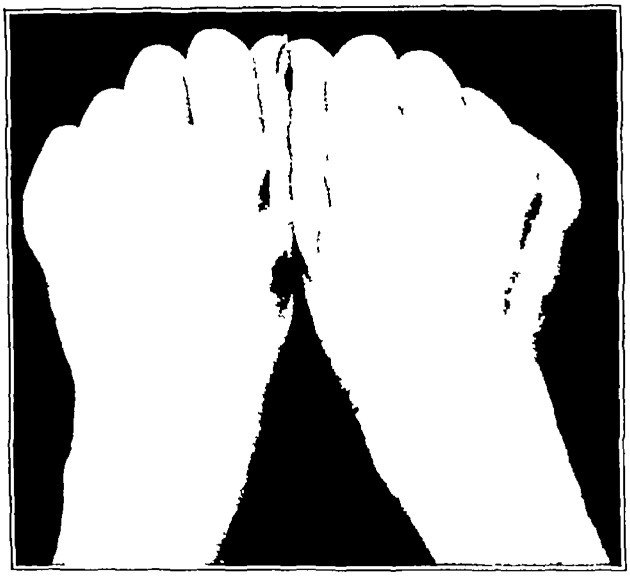

Fig. 2 (case 1).—The character of the skin on the two hands appears practically the same when the fingers are tightly flexed. There is no evidence of scar tissue.

Recently there came under our care a patient whose injuries were so severe and in whom the result of our treatment proved so remarkable and so satisfactory that we deem it worth while to report the case in detail and to point out the advantages of our method of treatment with normal horse serum.

CASE 5.—J. W., a young chemist, on April 19, 1928, was closing an electric switch in the wall controlling a motor-operated mixing tank in which there was a quantity of purified petroleum benzin, when an electric spark from the motor ignited the vapors, causing an explosion. The room in which this occurred was on the ground floor level of a small two story building. The flames cut off the exit, and were between the patient and a closed window. He jumped headlong through the fire and out through the window to the ground. First aid dressings of lime liniment were applied and he was immediately rushed to the Mack Hospital.

On admission, the patient was suffering from shock. Examination showed second degree burns of the palmar and extensor surfaces of both hands, and the flexor and extensor surfaces of both forearms, first degree burns of the entire face and head, a lacerated wound of the right palm, probably caused by the broken window, and abrasions of both knees. Chronic cardiac valvular disease was also noted, a result of rheumatic fever in childhood.

The burns were dressed with an antiseptic ointment, and morphine was administered hypodermically to control the intense pain in the hands. A prophylactic dose of 1,500 units of tetanus antitoxin was administered subcutaneously in the interscapular region to guard against possible tetanus infection in the lacerated palm of the right hand, which came in contact with street dirt when the patient struck the ground after his jump through the window. On the second night, the pain was still quite severe and the administration of morphine was repeated. On the third day the heart required digitalis, which was administered every four hours during the next four days. The condition of the heart at this time was due, in our opinion, to the toxemia resulting from the absorption of toxins from the burned areas.

On the fourth day the patient complained of considerable discomfort in the hands, and the temperature mounted to 101.2 F. At this time the fingers and hands were nearly one and a half times the normal size. We regret that we neglected to take photographs at that time. Following a consultation, we decided to use the serum treatment.

The ointment was removed and the hands and forearms of the patient were immersed in a bath of warm physiologic solution of sodium chloride for a period of three hours, after which all devitalized tissue which had been loosened by the prolonged bath was removed with forceps and scissors. An ordinary oil atomizer was sterilized and filled with the normal horse serum. Then the forearms, hands and fingers were thoroughly sprayed with the serum and protected with rubber tissue held in place with gauze bandages. The dressings were removed and the normal horse serum was reapplied twice daily. The face at this time was healing nicely and it was left exposed to the air, being protected where necessary by a thin layer of the antiseptic ointment.

Twenty-four hours after the initial serum treatment the patient's temperature dropped to 100 F. and he reported that his hands felt comfortable. On the second day of serum treatment, the temperature was down to 99.2 F., and on the third day of serum treatment the temperature was normal and remained normal during the remainder of the patient's stay in the hospital. On this day also the heart action had improved to such an extent that digitalis was discontinued. On the fifth day of the serum treatment the fingers on the left hand were healed sufficiently to warrant their being left unbandaged and the patient was therefore able on this day to feed himself for the first time since his admission. From this date, the patient made a rapid and uneventful recovery, which was complete and without any complications. He was discharged from the hospital completely cured, May 4, having been in the hospital a total of fifteen days. Treatment with normal horse serum had been carried out during the latter eleven days of his stay.

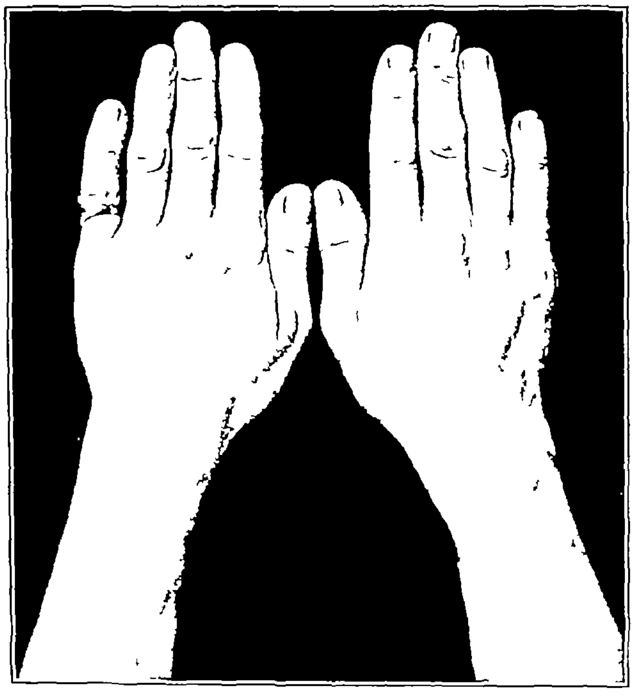

Fig. 3 (case 5).—Attention is called to the heavy transverse ridge in the thumb nails due to injury of the nail root by the burn. Hair has grown out from the new skin on the backs of the hands and the forearms.

By the term "completely cured" we mean that the entire burned areas were covered with new healthy epidermal tissue and that there was an entire absence of cicatricial tissue. The new tissue over the wounded area was a deep pink and was quite sensitive to heat and cold and to pressure. The color at the present time (five months after the injury) is fading out, as indicated in the accompanying photographs In figure 3, the heavy transverse ridge in the thumb nails may be noted This ridge indicates the severe injury to the root of the nail caused by the burn Similar ridges were present on the nails of the fingers, but they have grown out beyond the tips of the fingers and have been removed Hair has grown out from the new skin on the backs of the hands and fingers Figure 4 shows the most striking result of the serum treatment of this case The palmar surfaces of both hands are covered with strong, healthy tissue, and there is not even a suggestion of any scar tissue The patient has complete normal use of both hands, for there is entire absence of any contracture The lacerated wound at the base of the right thumb healed perfectly The flexor surface of the right wrist at the ulnar side is the only portion of the new tissue that now shows any color and at this location there is a triangular area of color which is still visible

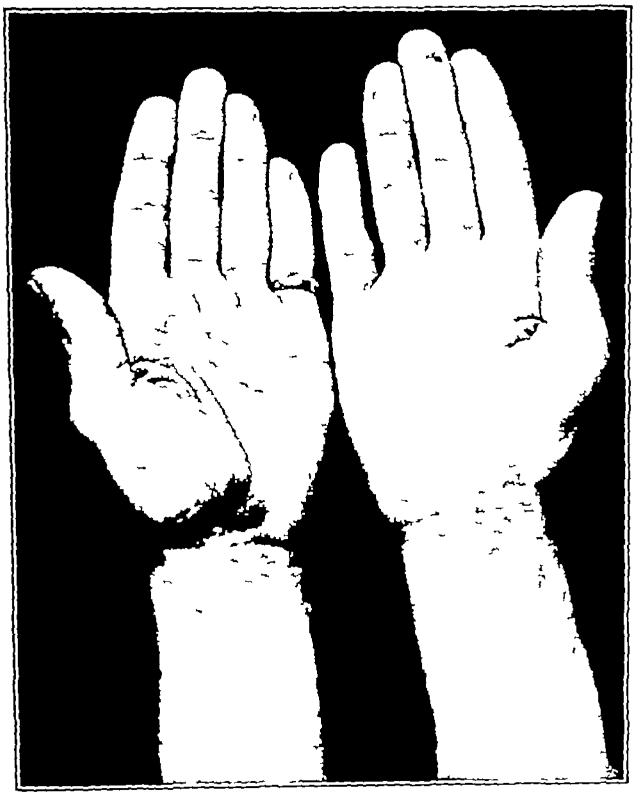

Fig 4 (case 5) —The palmar surfaces of both hands are covered with strong healthy tissue and there is no suggestion of any scar tissue There is a triangular area of color still visible in the new tissue at the ulnar side of the flexor surface of the right wrist.

Throughout the serum treatment of our cases of burns we have employed normal horse serum furnished by the Lederle Antitoxin Laboratories This is a sterile serum containing 0 35 per cent cresol as a preservative The bottle containing 100 cc offers a convenient means of transferring the serum to an atomizer It is said that normal horse serum increases the coagulability of the blood and when applied locally, exercises a hemostatic action in controlling hemorrhage It was the hemostatic action of the serum when applied to the oozing surface of a wound that suggested to Robinson s mind its possible beneficial action in the treatment of burns

COMMENT

The rationale of using normal horse serum in the treatment of burns is dependent on the fact that the tissue cells require a physiologic medium in which to multiply and build up the destroyed area, otherwise scar tissue will result Normal horse serum coagulates the exuding tissue plasma and holds it in contact with the living cells, which are thus provided with the necessary physiologic medium in which to multiply and rebuild the devitalized area by the formation of new, healthy epidermal tissue The cresol used as a preservative in the serum, acts as a mild antiseptic and tends to inhibit bacterial growth, thus minimizing the formation of pus and of scar tissue It is important to prevent drying of the tissues of the burned area, as otherwise the cells will die, and the normal horse serum should therefore be applied at least twice daily The use of rubber tissue[4] over the wounds prevents evaporation and thus insures prolonged action of the serum For burns involving an extensive surface area, the warm saline bath may advantageously be given prior to each application of the serum, and in such cases the serum may be applied three or four times daily Spraying affords a convenient method of applying the serum with a minimum of waste

The treatment of burns which we have outlined serves a fourfold purpose 1 The saline bath facilitates the removal of devitalized tissue 2 The saline bath removes by dialysis the toxins generated in the burned areas, and thus prevents their absorption and the development of toxemia In this connection, it should be emphasized that, when treatment with normal horse serum was started in the last case cited, the patient had a temperature of 101 2 F, which, in our opinion, resulted from the absorption of accumulated toxins As soon as the toxins were removed by the saline bath and all devitalized tissue was taken off, the temperature immediately dropped and reached normal three days later 3 The normal horse serum causes clotting of the exuding tissue plasma and thus provides the marginal and deeper tissue cells with a new protective film of coagulated tissue plasma free from accumulated toxins, so that the cells are fed with their natural physiologic food This makes it possible for the entire denuded area to be uniformly and rapidly built up with new healthy tissue, instead of the scar tissue that so often forms as a result of other methods of treatment 4 The cresol used as a preservative in the normal horse serum acts as a mild antiseptic and tends to inhibit bacterial growth, thus maintaining sterility of the wound and minimizing the formation of both pus and scar tissue

SUMMARY

1 The method of treating burns with normal horse serum as here described is simple and easily applied It does not soil bed linen or clothing

2 In our hands, this method has yielded far better end-results than any other method that we have employed for the treatment of burns due to fire, hot water or acids

3 The important advantages of this method of treating burns are (*a*) absence of scar tissue, (*b*) rapidity of formation of new epidermal tissue in all parts of the wound, (*c*) freedom from pain, (*d*) prevention of infection, and (*e*) elimination of toxemia by preventing the absorption of the toxins

4 Even when the destruction of tissue involves a large area the wound becomes covered with sound, healthy tissue and there is no contraction with result-

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[4] Surgical supply houses market this material under the name rubber dam in sheets of one square yard

ing deformity, splints, traction or skin grafts are not required

5 When burns are treated by our method, bacterial growth is inhibited by the cresol in the serum and pus formation is minimized

6 When burns of the skin bearing hair are treated with normal horse serum by our method the denuded area becomes covered with healthy epidermal tissue which again bears hair

7 We would emphasize the value of the preliminary bath of warm physiologic solution of sodium chloride It not only facilitates removal of the devitalized tissue but also prevents absorption of the toxins generated in the burned area

8 Normal horse serum containing cresol when sprayed on the burned area, coagulates the exuding tissue plasma and thus provides the healthy cells with physiologic food, so that the cells can proliferate and form new, healthy epidermal tissue

9 The serum should be applied at least twice daily to prevent drying of the tissues in the burned area, which would cause death of the cells

10 After the normal horse serum has been applied, the wounded surface is protected with rubber tissue which prevents evaporation and thus insures prolonged action of the serum

50 North Broadway

REPOSITORY INJECTIONS

HOW TO OBTAIN LASTING EFFECTS WITH INJECTED WATER-SOLUBLE MEDICAMENTS SUCH AS INSULIN AND EPINEPHRINE

CLAUSS BURKART STRAUCH, M D
MC GREGOR, MINN

The parenteral introduction of various drugs has of late years become more and more common Such injections, however, have the disadvantage that the drug effect is transitory, for, irrespective of the mode of injection, the medication reaches the blood stream relatively quickly and its effect is soon over This drawback is, of course, not significant under some conditions, as the use of a narcotic to deaden pain, or of a stimulant during collapse For many other purposes, however, as with glandular preparations, continuous action is much to be desired

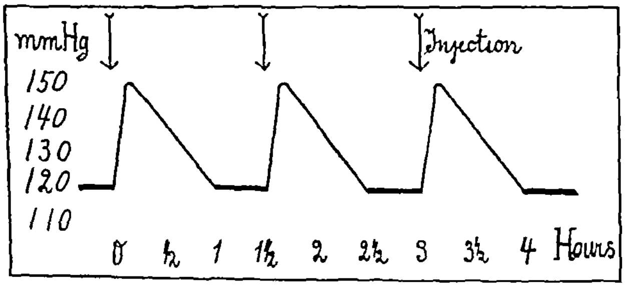

Fig 1 —Blood pressure curve after three subcutaneous injections of 1 cc each of epinephrine within four hours The arrows indicate the injections (Schematized in accordance with the normal curve of Dresel Ztschr f exper Path u Therap **22** 34 1921)

The transitory effect of hypodermic medication is well shown by two drugs, epinephrine and camphor Figure 1 illustrates the effect on blood pressure of three injections of 1 cc each of epinephrine given during a period of four hours It will be noted that each injection was followed by a rise in the blood pressure, but that this rise was of short duration Figure 2 illustrates the duration of action of an injection of 5 cc of camphor in oil, the length of drug action being measured by the excretion of glycuronic acid in the urine In this instance the relatively short period of drug action is again demonstrated It is true that hypodermic medication can be supplemented by oral administration, and that with some drugs having a cumulative action, such as digitalis, prolonged effects can be obtained Such instances are, however, rare

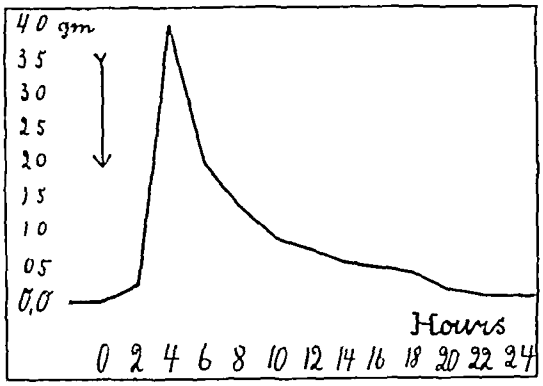

Fig 2 —Effect of camphor after injection of 5 cc of strong camphor liniment (measured by the elimination of glycuronic acid in the urine)

The present paper describes a method whereby a prolonged and uniform effect can be obtained by the parenteral introduction of a therapeutic agent No such method has been described heretofore, all previous hypodermic medication supposedly acting in the manner of a repository has consisted either of oil soluble substances (camphor) or of insoluble substances (mercury or bismuth) How brief the effect of a camphor repository is was shown in figure 2

A simple method which permits the prolongation of the effect over days and weeks of water soluble drugs has been perfected in conjunction with Dr H Bernhardt, assistant at the First Medical Clinic of the University of Berlin, Charite Hospital (medical director, Professor His), where, for the most part the clinical experiments were performed Some of our investigations have already been reported[1] As did Campbell[2] and others, we first attempted to obtain the desired results by various combinations of mucoid substances, agar-agar, gelatin and acacia These experiments were unsuccessful Fats and lipoids were also tried with similar results to those recorded by Hedvall[3] Somewhat more successful results were obtained with hydrous wool fat

The method finally selected was based on the following theoretical considerations A water in oil emulsion (a combination seldom employed in pharmacology, which usually employs an oil in water emulsion) has the property of enclosing the water taken up by the fat (fig 3) The subsequent absorption of the water is more or less hindered by the thin films of oil that sur-round each drop of water The delicacy of these films can be seen in figure 4 and better appreciated from the statement that 1 cc of oil can easily contain from 3 to 10 cc of water It is possible to maintain such an emulsion by the addition of small amounts of certain specific substances, termed emulsifier or emulgator

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[1] Bernhardt H and Strauch C B Die Oel Wasser und die Wasser Oel Emulsionen in ihrer Beziehung zur Medizin Ztschr f klin Med **104** 723 1926 Ueber parenterale Resorption von Fettstoffen ibid **106** 671 1927 Strauch C B and Bernhardt H Ueber parenterale Depots wasserloeslicher Medikamente ibid **104** 744 1926 Strauch C B Ueber die Bedingungen der Aufnahme und Abgabe von Wasser oder Medikamenten durch Salbengrundlagen Beit. z klin Chir **141** 358 1927

[2] Campbell J M H Lancet **1**: 777 (Oct. 6) 1923

[3] Hedvall Eric Essays thérapeutiques avec l insuline en emulsion huileuse Acta. med Scandinav **62**: 334 1925

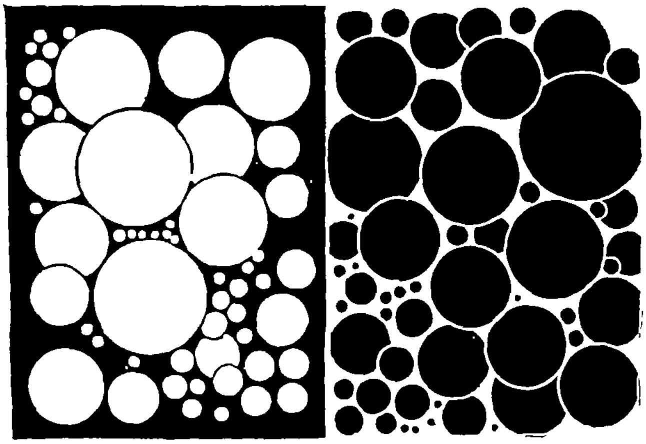

Fig 3 —Schematized comparison of the two main forms of emulsions showing the beginning of emulsification At a higher degree of homogenization the picture becomes more uniform Black shows the stained watery phase white the fatty phase

These synthetically prepared emulsions, however, are always quickly destroyed when injected into the tissues We have found still another group of substances, termed protective substances, which, when added to such water and oil mixtures with an emulgator, give a more or less stable emulsion which resists the action of the tissues

A highly concentrated solution, for example, epinephrine 1 50, has added to it about 25 per cent of its volume in olive oil Every single component has been sterilized separately The following is a typical formula concentrated and sterile solution of the drug

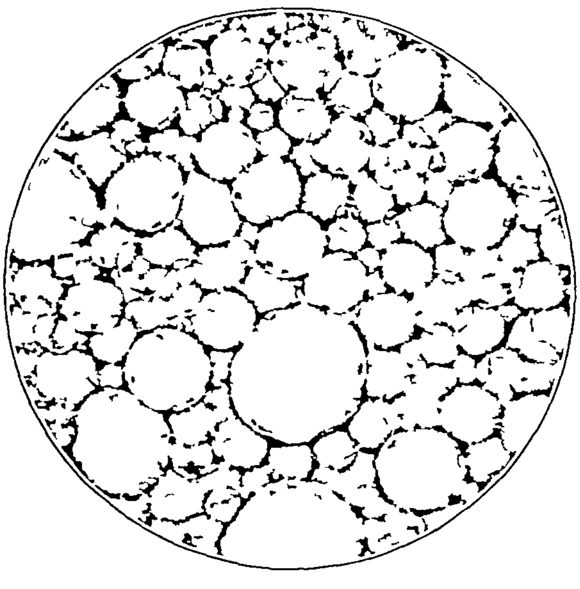

Fig 4 —Appearance of an emulsion × 1 000 (oil immersion)

10 cc sterile olive oil 2 5 cc sterile metacholestearin 0 2 Gm sterile myricin 0 3 Gm The components are combined and transformed carefully into a sterile and stable water in oil emulsion From 1 to 5 cc of the total volume is injected intramuscularly The result is a very gradual release of the epinephrine Absorption of the drug occurs every time one oil film is released from its enclosed droplet of epinephrine How quickly this release occurs is dependent on the amount of protective substance employed

The fact that the emulgator found most effective metacholestearin (Lifschuetz), and the best protective substance, a chemically pure wax, myricin (myricil palmitin acid ester), can be classed as more or less physiologic, permits the assumption that similar conditions also play a role in the membrane formation of body cells Clowes [4] first pointed out the significance of the emulsion process in cell life

These two substances (emulgator and protective substance) have such an elective effect on the surface energy of oil that we were able to demonstrate further that they regulate the separation of an oil-suspended pulverous medicament after injection into the body in minute additions like a specific brake or rein (stabilized suspensions) We were thus in the position of being able to produce repositories with pulverous as well as water-dissolved medicaments

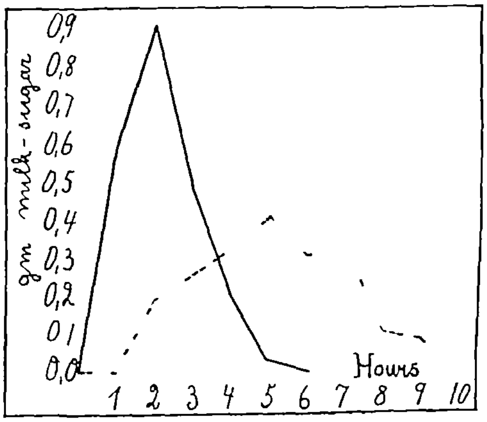

Fig 5 —Lactose elimination curve after subcutaneous injection of 30 cc of 9 2 per cent lactose solution solid line without the addition of 10 drops of epinephrine broken line with epinephrine (According to Klapp Deutsche Ztschr f Chir **71** 197)

That such combinations are effective is shown by the following experimental and clinical data A number of mice were injected with 1 cc of an emulsion prepared according to the method described This emulsion contained 75 per cent of a 1 100 solution of methylene blue (methylthionine chloride U S P) Blotting paper was kept on the bottom of the animals' cages in order to soak up the stained urine After the injection the blotting paper, which was renewed daily, showed a fairly uniform methylene blue stain over a period of several weeks

The lethal dose of strychnine nitrate for a mouse weighing 13 Gm is 0 2 mg If ten times the lethal dose (2 25 mg) is given at one time in emulsion form the animal does not die, but even as late as four days after injection shows distinct tetanic spasms following light taps on the table, this being an evidence of continuing strychnine effect With morphine repositories containing many times the lethal dose and administered to mice, the typical elevation of the tail was maintained for about four days after the injection [5]

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[4] Clowes G H A Protoplasmic Equilibrium J phys chem **20**: 407 1916

[5] These and other animal experiments were demonstrated by Dr H Bernhardt by means of a film at the Congress for Internal Medicine at Wiesbaden in April 1928

Quantitative results are shown in figures 5 and 6 As is shown in figure 5, a dog received an injection containing 30 cc of a 9 2 per cent solution of lactose without, and at a later period with the addition of 10 drops of epinephrine The elimination of the lactose is shown to have continued for six hours without epinephrine and for ten hours when epinephrine was added Figure 6 shows the results obtained when a dog was given an injection of a repository emulsion containing 45 3 Gm of lactose Elimination of the lactose was not complete even after fifteen days

In a further experiment two completely diabetic dogs, made so by complete extirpation of the pancreas, were kept alive for eight weeks with repository injections of 200 units of insulin given every five days

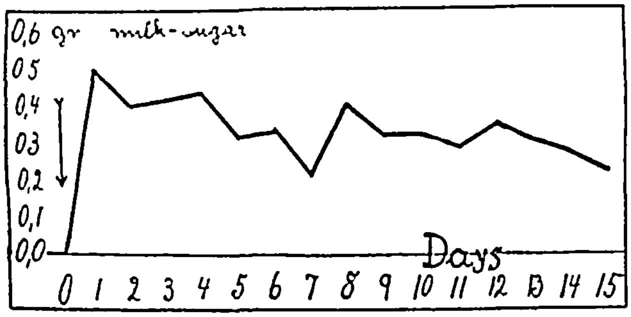

Fig 6—Lactose elimination curve after injection into a dog of 45 3 Gm. of lactose as a repository

The foregoing as well as the following experiments were made with emulsions and with stabilized suspensions Each has something in its favor Since the preparations resembling ointments are rather viscid, they were put into tubes in sterilized form and easily transferred for injection into a modified syringe

From the clinical standpoint repository injections were prepared and administered, atropine, strychnine, ergot, cardiac remedies, iodine, vaccines and irritants being used For the present these experiments will not be discussed Figure 7 shows the result of using an iodine repository, the lasting effect of which can be exactly determined

One interesting series of observations concerns the use of insulin as a repository injection More than 100 patients have been treated with insulin repository injections of from 100 to 1,000 units of insulin each Of this number nine patients were treated over a period of six months In preparing the injection insulin powder was employed, 1 cc of the suspension equaling 200 units of insulin Injections were given every five to seven days The hypoglycemia occasionally noticed on the first day and the evidences of cessation of drug action occasionally noticed on the sixth day were controlled by increasing or decreasing the carbohydrate intake (fig 8) The acidosis was frequently more effectively influenced than was the blood sugar Some patients reacted in much better fashion to the injection of repositories than to single injections Variations in the physiologic strength of insulin powder and the instability of the repository preparations after two or three months is still an obstacle to its general use

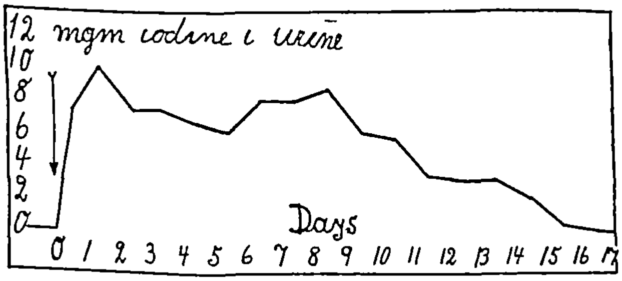

Fig 7—Effect of iodine repository

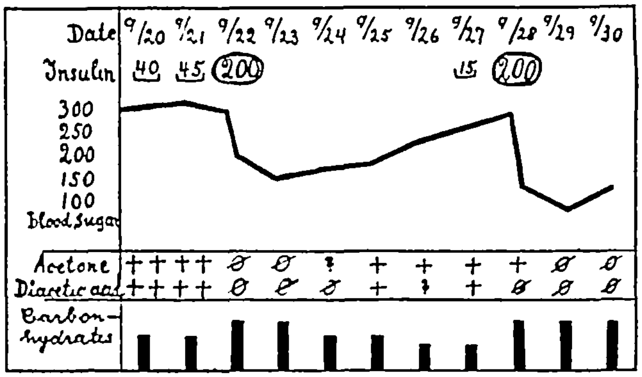

Fig 8—Effect of insulin repository (200 units is equal to 1 cc) + means positive 0 negative

Twenty-five patients with such conditions as pneumonia and cardiac collapse were given epinephrine repository injections, the repositories being arranged to have an action lasting from twenty-four to forty-eight hours (fig 9) For such conditions as Addison's disease, the formula can be so arranged that much longer action is secured

Pituitary extract fifteen times the usual strength was prepared for us, and repository injections of eight times the usual dose were prepared and administered in eight cases of diabetes insipidus The patients were relieved of thirst for from three to six days and the urine excretion decreased (fig 10)

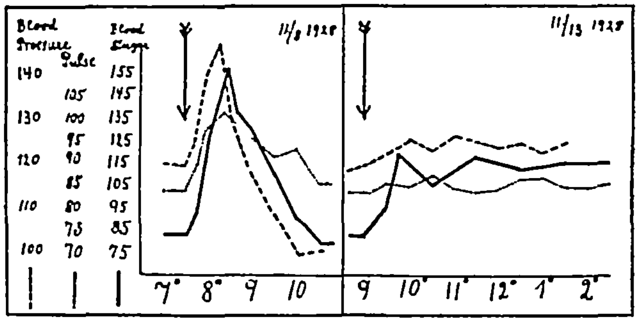

Fig 9—Comparative curves of effect of epinephrine left, subcutaneous injection of 1 mg of epinephrine in solution right, 3 mg of epinephrine as a repository, showing effect in the same patient in the fasting condition

The question of the general effect of repository injections and their absorbability has been studied and previously reported on At times after injection the patient complains of feeling a knot at the point of injection, but we have not observed an abscess, acute inflammatory reaction, pain or other sign of injury after any of the injections either in man or in animals A dosage as high as 180 cc given to a dog is absorbed within four months The sterility of the fatty repository preparations can, of course, be readily accomplished and readily checked

The objection that under certain conditions the repositories may separate very rapidly into compound parts, as when the patient has a fever or after improper preservation, has to be taken more seriously In general, it can be said that the repository acts in the body similarly to a wound-up clock movement that requires a certain time to run down For the same reason, the individual ability for absorption has a comparatively small influence on the duration of the effect As a matter of fact, up to now we have never observed any danger through an overdose

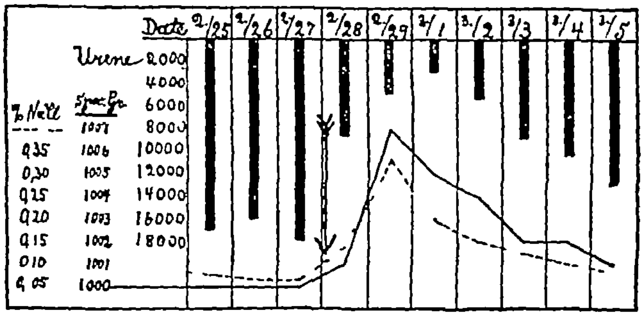

Fig 10—Effect of pituitary repository in a case of diabetes insipidus postencephalitis.

I believe that the method described opens a new era in injection therapy The repository injections will supply to the body a substitute for the secretion of the endocrine glands of a similarly enduring and well regulated dosage and of far more varied effect

Clinical Notes, Suggestions and New Instruments

GRADENIGO S SYNDROME

Garnett Cheney M D San Francisco

Gradenigo's syndrome consists of a triad of symptoms which were first described by Gradenigo in 1904 They are acute suppurative otitis media, severe temporoparietal pain, and a paresis or paralysis of the abducens nerve on the same side The syndrome has been frequently reported abroad, and recently several articles on the subject have appeared in this country, but these have been almost entirely confined to the special journals on otology and ophthalmology The clinical picture is of general interest, as the pain is in the form of a trigeminal neuralgia, except that it is limited to the first division of the fifth nerve and may persist for weeks or months after the discharge from the ear has ceased. It is also important to recognize the ocular palsy, which usually occurs between the fourth and sixth weeks, as a part of the same picture, and to know that it nearly always clears up Sears[1] has recently given an excellent survey of the syndrome.

REPORT OF CASE

Mrs E. L S, aged 60, an American housewife, first came under medical observation March 22, 1928, because of severe pain in the left ear and jaw of two days' duration. The family history seemed irrelevant She had not had any pregnancies Her husband was living and in fair health. The only noteworthy event in her past history, aside from a decided hysterical trend, was the appearance of a fiery red lesion on her neck three months previously This disappeared within two weeks but was followed by trouble with her teeth. She had had some teeth crowned by a dentist well known through his advertisements She continued to have occasional aching, particularly in the left upper jaw, previous to her present complaint. For two days she had suffered such pains in her left ear that she was beside herself. As she was a Christian scientist she had not permitted her husband to call a physician.

The patient was well developed and well nourished, but her manner was uncooperative and hysterical The pulse rate was 68, and the temperature was 99 2 F The appearance of the eyes and pupils was not unusual The external meatus of the left ear was red, puffy and very tender, but no discharge was noted. The teeth were in poor condition, several exuding pus from the sockets The breath was foul and the tongue thickly coated The tonsils and throat did not show any evidence of infection The skin over the lower left side of the face and neck was red and rough. There were no enlarged cervical glands Examination of the chest, heart, lungs, breasts, abdomen, spine, reflexes and joints did not disclose anything remarkable The blood pressure was 118 systolic and 78 diastolic. The urine and the Kahn test for syphilis were negative. An ear consultant was called in who opened the left ear drum, permitting the free discharge of a small amount of thin pus, and the patient felt considerably relieved

The next day she had an erysipelas of the left side of the face, ear and tongue, which reached its height two days later and gradually subsided The temperature was not more than 100 F During this time she complained of severe pain in the left ear and the left temple, although the ear was draining well and there was no pronounced mastoid tenderness A week after she was first seen the pain in the left ear became excruciating and it was also felt in the left temporal and parietal regions Skin hyperesthesia was marked over these areas Large doses of amidopyrine and codeine were necessary to control the pain. A complete blood count at this time was normal, and the temperature was 99.2 F During the next four weeks she suffered from similar pains over the same region She described a constant dull ache emanating from within the ear itself, a throbbing pain and unbearable attacks of terrific, shooting knifelike pain running above her left ear Her suffering was allayed only by the constant use of drugs

On the thirty-sixth day of her illness, the patient developed a weakness of the external rectus muscle of the left eye which persisted for two weeks The pain persisted and she felt that she was "at the end of her rope" She threatened suicide on three occasions. The ear had ceased to drain. She had had several abscessed teeth removed, but the neuralgia persisted a month longer, the attacks gradually growing less severe and less frequent The total course of her illness was three months, but even after this time she used codeine occasionally for persistent neuralgia Six months later she was reported free of pain.

Shreve Building

TULAREMIA FROM THE MUSKRAT

Harold Schwartz M D Butte Mont

The occurrence of tularemia in man is rapidly assuming more importance in the field of medicine The increasing and widespread incidence of tularemia in the animal kingdom and the discovery of new sources of infection adds further interest to this disease

The cases of ulceroglandular tularemia reported here reveal a new source of infection both are directly attributable to the muskrat, having resulted from the skinning of a muskrat to obtain the pelt

REPORT OF CASES

Case 1.—A. K., aged 29, a Japanese section laborer who had lived in the United States for the past ten years and who had not had any previous illness, on Oct. 28, 1928, while camping near Deer Lodge, Mont., caught a muskrat in a pond along the railroad and with his companion skinned the muskrat to obtain the pelt. November 1, forty-eight hours later, he noticed a red streak on his left arm, extending from the epitrochlear gland to the axilla. The axillary glands were swollen and tender A few hours later he noticed a blister-like sore on the inner surface of the middle finger of the left hand. He felt feverish for two days and had some malaise. He was confined to bed for one day He did not have any chills or headache. The swelling of the epitrochlear gland and of the axillary glands increased in size for four or five days and then remained stationary The lesion on the finger was entirely healed on November 20 There was no history of previous injury to the hand There was no secondary rise in temperature, and no skin eruption was noticed The patient resumed his work after three days

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[1] Sears W H Laryngoscope 37 33 (Jan.) 1927

At examination, November 28, the patient's general appearance was good The temperature was 99 F, the pulse rate, 76 The condition of the heart and lungs was excellent The blood pressure was normal The patient had a healed scarred lesion on the inner surface of the middle finger of the left hand, about three fourths by one-half inch (19 by 13 mm) The epitrochlear gland was enlarged, 1 by one third inch (25 by 8 mm) The axillary glands were enlarged in a mass about the size of a small orange, and were tender to the touch There was no evidence of suppuration or of other glandular enlargement Subcutaneous nodules were not present on the arm or forearm From the history and examination a diagnosis of the ulceroglandular type of tularemia was made This was confirmed, November 30, by a report from the state hygienic laboratory showing complete agglutination of *Bacterium tularense* in dilution 1 640

Case 2—T A, aged 30, a Japanese section laborer, whose history was practically the same as that of patient 1 as to the time of onset and the beginning symptoms, had, however, an unhealed abrasion on his finger at the time he assisted in skinning the muskrat The patient observed that his symptoms began four hours earlier than those in patient 1 Soreness and swelling in the left axilla were first noticed, followed in twenty-four hours by soreness over the middle joint of the left index finger A red streak from the epitrochlear region to the axilla appeared at the same time The patient had chills the first day, fever for two days and felt ill enough to be confined to bed for two days He had headache for a period of two weeks The glands in the axilla increased in size until the fifth day, after which they remained stationary The finger healed in fifteen days, after ulcerating and liberating a small necrotic core. The patient resumed work on the third day

At examination, Nov 28, 1928, the patient's general appearance was good The temperature was 98 6 F, the pulse, 74 The heart and lungs were normal There was a healed scarred lesion about one-half inch (13 mm) in diameter over the middle joint of the index finger on the left hand The left epitrochlear gland was enlarged to about one-half by one fourth inch (13 by 6 mm) The axillary glands were enlarged in a mass the size of an egg, and tenderness was noticed There was no evidence of suppuration

The diagnosis of tularemia (ulceroglandular type) was confirmed by a report on the blood from the state hygienic laboratory, November 30, to the effect that there was agglutination with *B tularense* in 1 320 dilution, and partial agglutination in 1 640 dilution

COMMENT

In a review of the literature, I failed to find any reference to the muskrat as a source of human infection with tularemia Inquiries were addressed to the Montana State Hygienic Laboratory and to the United States Hygienic Laboratory

Dr McCoy of the Hygienic Laboratory replied 'The cases of tularemia you mention are, so far as I know, the first definitely attributable to muskrat infection, although we have known for some time that the muskrat was susceptible."

Dr Cogswell of the state hygienic laboratory of Montana replied "This is the first report of this disease in Montana having been contracted from muskrats—probably the first in the country ' Later, he forwarded a communication from E M Wade, chief of laboratories in Minnesota, relative to experimental work on the muskrat, which is of interest in this connection "Our experience with muskrats in tularemia has been confined to experimental work We have inoculated subcutaneously and through skin abrasion several muskrats, all of which succumbed to the disease in two to five days All of these animals had on autopsy typical lesions of tularemia in the spleen and liver, as well as inguinal glands Material from these organs as well as the heart s blood of the muskrats inoculated into guinea-pigs produced typical lesions and death of the guinea pigs

How the muskrat in nature becomes infected with tularemia is a future problem for the scientific investigator

58 West Quartz Street

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies A copy of the rules on which the Council bases its action will be sent on application

W A Puckner, Secretary

LENIGALLOL—Pyrogallolis Triacetas—Triacetylpyrogallol $C_6H_3(CH_3CO_2)_3$—Pyrogallol triacetate, obtained by replacing the hydroxyl groups of pyrogallol with acetate groups

Actions and Uses—Lenigallol as such is said to be nonpoisonous and nonirritating, but it produces a mild and painless corrosive effect by the gradual liberation of pyrogallol (See note under Creosote and Guaiacol Compounds)

It is introduced as a substitute for pyrogallol in psoriasis, lupus, acute and subacute eczema of children and other skin diseases

Dosage—In 5 to 10 per cent ointment with zinc oxide

Manufactured by Knoll A-G Ludwigshafen a Rh, Germany (E Bilhuber, Inc, New York distributor) No U S patent or trademark.

Lenigallol is prepared by boiling 10 parts of pyrogallol 1 part sodium acetate and 25 parts of acetic anhydride for two hours and washing the crystalline product on a filter with water

It is a white crystalline powder melting at 165 C. It is insoluble in water but soluble with decomposition in warm aqueous alkalies

Lenigallol is incompatible with alkalis, strong acids and oxidizing agents

BISMUTH SODIUM TARTRATE-SEARLE (See The Journal, June 30, 1928, p 2103) The following dosage form has been accepted

Solution Bismuth Sodium Tartrate Searle 1 5 per cent An aqueous solution containing bismuth sodium tartrate Searle 0 015 Gm, benzyl alcohol 0 02 Gm and sucrose 0.25 Gm, in one cubic centimeter

REPORTS OF THE COUNCIL

The Council has authorized the publication of the following report

W A Puckner, Secretary

NATIONAL RADIUM EMANATOR AND SAUBERMANN RADIUM EMANATION ACTIVATOR OMITTED FROM N N R

The National Radium Emanator, marketed by the National Radium Products Company, and the Saubermann Radium Emanation Activator, marketed by Radium Limited, are appliances for impregnating drinking water with radon (radium emanation) in dosages ranging from 50,000 to 200,000 mache units in the case of the former, and 10,000 to 100,000 mache units in the case of the latter The acceptance of both these products expiring this year, the firms were asked to submit evidence in favor of their continued inclusion in New and Nonofficial Remedies The National Radium Products Company submitted an advertising circular which was in effect an indirect advertisement to the public and which made claims far in excess of those previously permitted by the Council for radium and radium preparations Radium Limited failed to respond to requests for the current advertising

For some time the Council has been dubious of the therapeutic value of radioactive drinking water In 1927 the Council decided to continue the acceptance of preparations designed for the internal use of radium only on condition that the claims for them were limited to recommendations for trial in chronic arthritis, gout, neuritis and high blood pressure In consideration of the claims made for the National Radium Emanator and of the failure of the manufacturers of the Saubermann Radium Emanation Activator to submit the present advertising claims to the Council for review, and because no further acceptable evidence has become available, the Council voted to omit these products from New and Nonofficial Remedies and not to accept further apparatus for the activation of drinking water until convincing evidence for the therapeutic value of the internal use of radon becomes available

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SATURDAY, APRIL 6, 1929

STARVATION AS A THERAPY

Fasting as a cure of diseases other than those due to overeating runs back to antiquity. It is frequently bound up with religious practices and prayer under the assumption that abstinence from food "purifies" the body and renders it less susceptible to the influences of evil and more susceptible to the influences of good. When fasting is united with prayer one cannot know whether the favorable outcome is due to the fasting or to the prayer. In a recent address before the Medical Society of London, Dr. Edmund Spriggs[1] reviews the history of fasting as a therapy in earlier times, the modern indications for fasting in disease, and the dangers involved in the therapy of fasting. The physical, chemical and mental changes involved in prolonged starvation have been subjected to excellent studies both on man and on animals in recent years. Organs lose weight, not uniformly, and some, such as the heart and brain, lose at a much slower rate than organs such as the pancreas, liver and spleen, and the skeletal muscles. The basal metabolic rate and the blood pressure are gradually lowered during a prolonged fast. Complete starvation, particularly in an obese person, leads to a mild degree of acidosis. The changes in the blood during starvation are not great. There is a tendency to a slight increase of the nonprotein nitrogen and slight but not consistent or persistent decrease in the blood sugar. A healthy, well nourished man may fast for from thirty to forty days without demonstrable permanent injury, and dogs may fast without apparent injury for a much longer time. All this, of course, is under conditions when the individual receives a liberal allowance of water. After the rapid loss of weight during the first few days of fasting, an adult person on complete starvation may lose weight at the rate of about half a pound a day when no excessive physical work is being done. Despite the complete absence of food in the alimentary canal for from thirty to forty or more days, the alimentary canal still harbors at the end the flora common for this organ. Fasting for the purpose of sterilization of the alimentary canal is a failure. Complete starvation is not painful. The essential subjective symptoms are fatigue, and the predominance in consciousness of thought of food and eating. The sex urge is decreased. Dr. Spriggs refers to the wartime undernutrition experience of central Europe. Good clinical studies of these conditions have been reported. At no time, of course, was there complete starvation in Germany or Austria. There was rather prolonged undernutrition and probably, in some cases, there were qualitative deficiencies in the diet, accompanied by unusual mental stress and anxiety, worry and fear. Under this restricted food intake in central Europe cases of diabetes, gout and obesity were greatly improved or decreased in number, while nervous disorders increased, as did tuberculosis and anemia. Patients with myxedema appeared to do badly. Chronic diarrheas and digestive disorders were increased, but this may have been due to the abnormal character of the available food rather than to the partial starvation.

Dr. Spriggs outlines the results of the clinical experience with starvation in local diseases of the alimentary canal, in epilepsy, in obesity, in diabetes, and in diseases of the circulation. He concludes that complete fasting is beneficial in appendicitis, peritonitis and ulcers, largely on the basis of the rest of the digestive organs afforded by the absence of food. The reasons assigned for the apparent benefits of fasting in alimentary canal disorders do not seem convincing, since it is now known that the digestive glands continue to secrete and the alimentary canal continues to exhibit motility all through a prolonged fast. Short complete fasts of from two to three days are said to be valuable in a number of other diseases, such as pneumonia, severe fevers, acute nephritis, chronic uremia, migraine, hyperthyroidism, local infections, phlebitis, rheumatism, rickets, and the vomiting of pregnancy. A number of physicians have reported diminution in the number and intensity of epileptic attacks in patients with idiopathic epilepsy during fasting. This appears to be due, not to the fasting directly, but to the acidosis accompanying the fast. On the resumption of a normal diet the condition of the patient returns to the original state. Dr. Spriggs discusses in greater detail the regimen of fasting in obesity. He recommends not complete abstinence from food but a severe restriction of the calory intake to a level of from 1,000 to 1,300 calories. This restriction should be horizontal rather than vertical, so that the patient obtains some of every ingredient necessary for the body welfare. The calory restriction is usually coupled with a definite increase in physical activity. Dr. Spriggs appears to have had success with this therapy not only with those obese from excessive eating but even in those obese in consequence of apparently hereditary factors ("endogenous" obesity). The pains and discomforts that some of these patients may exhibit after ten days or two weeks on this low calory intake are said to be quickly relieved by a meal "Serious symptoms seldom arise during the treatment, and those formerly present generally disappear Especially striking is the loss of breathlessness" This is ascribed to the removal of fatty tissue among and within the muscle fibers of the heart Anemia, it is reported, does not develop under this regimen Dr Spriggs remarks that obesity is often complicated by other disorders, and as a general rule after treatment by starvation the accompanying disease is improved Two conditions especially can nearly always be treated in this way circulatory disorders and mild glycosuria Patients with high blood pressure benefit almost invariably by reduction in weight, if they are overweight, and in the majority of other patients the blood pressure is also reduced Dr Spriggs considers that a temporary short fast is still of value in diabetes, and mild diabetes may be controlled by moderate calory restriction without the use of insulin He points out that children and cachectic and tuberculous individuals should not be deprived of food for more than a comparatively short period

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[1] Spriggs, Edmund: Lancet 1: 485 (March 9) 1929.

Except in cases of obesity clearly due to overeating or underexercise, the fasting therapy is obviously not a cure-all but merely an aid to other remedial measures The complications that may arise in a prolonged fast and the dangers to life and health that may eventuate in a starving person who is sick to begin with are such that fasting as a therapy is not safe except in the hands of competent physicians

According to Dr Spriggs, fasting in an otherwise healthy person decreases resistance to infectious diseases This may be seriously questioned, at least in cases of complete fasting not extending over longer periods than from fifteen to thirty days As to the ways in which fasting may improve the general body health, there is little reliable information except for those obviously obese from overeating, in which case it may be a matter of less work for the heart, lessened tendency to fatty infiltration of essential tissues, and lessened strain on the pancreas and the liver Dr Kunde[2] has shown that in complete fasts of fifteen days or more in man and from thirty to fifty days in dogs there is an increase in the basal metabolic rate extending over many months after the fast has been broken In dogs there is also an increased secretion of gastric juice and greater economy in the utilization of nutrients by the tissues If these results should be confirmed and extended, some of the apparent benefits from fasting may be rendered understandable on these lines Further, since in fasting the glandular tissues, among them the liver, pancreas, gastro-intestinal mucosa, thyroids and gonads, suffer great loss of weight, it is not improbable that in realimentation these organs respond with increased cell division and therefore may be said to be partly rejuvenated This matter requires further investigation before it can be put forth as a basis for fasting therapy

It has been suggested that nature itself points toward a fasting therapy in those diseases that are accompanied by decreased hunger and appetite But the success of the newer regimen of "feeding fevers" questions the inference The ills of overeating and the dangers of partial starvation are relative, and excessive claims are advanced in both directions

Among some people in this country, fasting as a road to health has become an unscientific if not an injurious fad On the other hand, some physicians go to the other extreme in holding that short periods of complete abstinence from food, and longer periods of severe restriction in calory intake, are always dangerous proceedings Some of Dr Sprigg's conclusions are still tentative More controlled observations both in the clinic and in the laboratory are needed before the final word can be said on the value and the limitations of fasting But if there is real albeit limited merit in the fasting therapy, its aroma of cultism and occultism is no deterrant

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[2] Kunde M M J Metab Research 3 399 (March) 1923 Am J Physiol 68 389 (April) 1924

VITAMIN CONTENT OF TREATED TOMATOES AND ASPARAGUS

In 1927 The Journal called attention editorially to the ethylene treatment of fruits and certain vegetables[1] and pointed out the necessity of research to determine the possible effect of ethylene on the vitamin content of such products as tomatoes Since then the ethylene treatment of fruits and vegetables has received considerable publicity and its use is increasing There appear to be two types of ethylene treatment,[2] one in which the ethylene seems to be used primarily for artificial coloration of oranges and lemons as a means of evading the proscriptions of the Food and Drugs Act against the artificial coloration of citrus fruits by dyes, even though harmless The position of the government in this respect is perhaps inconsistent, in view of the fact that the work was done by government experts in collaboration with citrus fruit growers' organizations The other type of ethylene treatment is that advocated by Harvey and his co-workers at the University of Minnesota, who have maintained that certain fruits (other than the citrus) and vegetables such as celery and tomatoes, when subjected to a sufficient concentration of ethylene, can be ripened as well as colored[3]

During the summer of 1928 an announcement was made by M F Babb that celery bleached by ethylene was not different in vitamin B content[4] from ordinary blanched celery, though the complete data on which this statement was based were not published

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[1] Artificial Ripening of Fruits by Ethylene editorial, J A M A 89 792 (Sept. 3) 1927

[2] Artificial Coloration of Citrus Fruits editorial, J A M A. 89: 1875 (Nov 26) 1927

[3] Recent reviews are given by Harvey R B Artificial Ripening of Fruits and Vegetables, Bull 247 Univ Minnesota Agric. Exper Sta, October 1928

[4] Vitamin B Content of Artificially (Ethylene) Ripened Celery J. A. M. A. 91: 965 (Sept. 29) 1928 Babb M F Effect of Ethylene upon the Vitamin B Content of Celery Science Sept 7, 1928 p 231

Now comes the publication of House, Nelson and Haber,[5] which answers questions first propounded by The Journal in reference to the vitamin content as it affects tomatoes These investigators, from the Iowa Agricultural Experiment Station, have made a comparison of the vitamin A, B and C content of green, air ripened, ethylene ripened and vine ripened tomatoes They conclude that no difference was apparent in the vitamin B content of these various types of tomatoes The vitamin A content of ripened tomatoes was found to be greater than that of the green mature fruit, and the same quantity of vitamin A was developed in the tomatoes regardless of the method of ripening employed Of particular interest to physicians is the vitamin C content for which tomatoes are generally prescribed in a diet The Iowa workers found green tomatoes to be relatively poor in vitamin C content, air ripened and ethylene ripened tomatoes were richer in this vitamin than the green fruit On the other hand, the vine ripened tomatoes were superior in vitamin C content to artificial ripened fruit or to green tomatoes This bears out the recommendation of The Journal when it first commented on the ethylene treatment of fruits, namely, that until investigation showed otherwise, the use of vitamin-containing products in as near a "naturally ripened" condition as possible should be encouraged when used for prophylaxis against avitaminosis

In the same issue of the *Journal of Biological Chemistry* as the report on the investigation of treated tomatoes appears a report from research workers at Michigan State College on the association of vitamin A with greenness in plant tissue[6] In the case of green asparagus, whether freshly cooked or canned, there was demonstrated the presence of vitamin A in sufficient quantities to promote health and growth when fed daily to albino rats Bleached asparagus, on the contrary, gave no stimulant to health and growth when fed to experimental animals They died as rapidly on the vitamin A free diet containing culinary "white" asparagus[7] as the negative controls Crist and Dye are of the opinion that a positive relationship exists between chlorophyll development and vitamin A content Whether or not this association is unalterably one of cause and effect is a question still to be answered The answer probably hinges on the experimental task of procuring plant tissue which is not green but the chemical composition of which will not introduce factors that complicate the results

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[5] House Margaret C Nelson P Mabel and Haber E. S The Vitamin A B and C Content of Artificially Versus Naturally Ripened Tomatoes J Biol Chem. 81 495 (March) 1929

[6] Crist, J W and Dye, Marie I The Association of Vitamin A with Greenness in Plant Tissue II The Vitamin A Content of Asparagus J Biol. Chem. 81 525 (March) 1929

[7] By bleaching the authors mean that the tissue has not been allowed to become green. This condition is obtained by covering the stalks with soil and cutting them just before they emerge above the ground.

Current Comment

DEDUCTIBILITY OF TRAVELING EXPENSES CONFIRMED

The Commissioner of Internal Revenue has acquiesced[1] in the decisions of the Board of Tax Appeals[2] in which the board held that a physician in computing his federal income taxes may deduct as a professional expense the reasonable cost of travel, including railroad fares, Pullman accommodations, room and board, incident to attendance at meetings of medical organizations of which he is a member The commissioner's acquiescence marks the end of the controversy by a decision in favor of the medical profession. To those physicians who in 1926 and thereafter paid increased federal income taxes because of the decision of the Commissioner of Internal Revenue in 1922 denying the deductibility of traveling expenses, the way is now open to obtain refunds of the excess paid Presumably, however, the amount claimable as a refund will ordinarily be too small in individual cases to warrant the trouble incident to obtaining repayment If the amount involved is sufficiently large to justify a physician in applying for a refund, he should obtain from the collector of internal revenue to whom the excess taxes were paid a copy of form number 843, execute it before a notary public or other officer authorized to administer oaths, and file it with the collector to whom payments were made No application should be made, however, unless the physician is prepared to verify his claim by adequate evidence, in addition to his own affidavit, if called on to do so It is presumed that the Commissioner of Internal Revenue will exercise a reasonable discretion, with respect to such demands, *but nothing will be gained by submitting claims that* cannot be reasonably well verified

S E BALL AND OFFICIAL INCOMPETENCE

Samuel E Ball, quack and ex-"patent medicine" manufacturer, who operates noisily from Excelsior Springs, Missouri, has just scored a triumph that is inimical to the public welfare Ball conducts what he is pleased to call the "Ball Health School" Ball's quackery has long been a stench in Missouri, and finally, in November, 1926, the state board of health revoked Ball's license following a hearing in which Ball was charged with unprofessional conduct in soliciting patients at railroad stations, with paying taxicab drivers for sending patients to his quackatorium, and with paying others in nearby cities commissions for patients that were sent to him The Missouri state law specifically defines the soliciting of patronage by agents as constituting unprofessional and dishonorable conduct and the law also authorizes the state board to revoke physicians' licenses for such conduct Following the revocation of his license, Ball appealed to the circuit court for a review of the findings and that court restored Ball's license Following this, the state board of health appealed to the supreme court Now, the Missouri supreme court has perforce affirmed the order of the circuit court to restore the license The supreme court's decision, it seems, is based on the failure of the board of health to enter in its records the specific ground on which it revoked Ball's license Judge Blair, who wrote the opinion, is said to state that the evidence shows without contradiction that solicitors or runners *were* employed to meet trains and interurban cars in Excelsior Springs to solicit persons to go to Ball's institution, which was conducted by a company in which Ball and his wife owned 93 per cent of the stock The supreme court further stated that, in its opinion, while it was satisfied that the evidence would have justified a finding by the state board that Ball was guilty of unprofessional and dishonorable conduct, nevertheless the court was "unable to see from the record made by the board itself that it ever made any such findings"! In view of the facts cited, one wonders whether the state board's action against Ball was a theatrical gesture

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[1] Internal Revenue Bulletin 8 12 1 (March 25) 1929

[2] Cecil M. Jack v Commissioner 13 B T A. *726* J Bentley Squier v Commissioner 13 B T A. 1223

ORAL ADMINISTRATION OF TYPHOID VACCINE

Almost twenty-five years has passed since Almroth Wright made the first experiment in immunizing human subjects against typhoid by the oral route He used a heat killed vaccine and estimated the success of his experiment by changes induced in the bactericidal power of the blood In the seven subjects treated, bactericidal power was increased in three and diminished in four These negative results seem to have discouraged further experiment for some years French investigators, however, began to experiment with oral immunization in animals shortly before the war, notably Besredka, who was able to achieve successful results with paratyphoid vaccine in rabbits by preparing the rabbit's intestine with a 10 cc dose of bile Besredka's experiments were interrupted by the war but were resumed as soon as he returned to civil life The first clinical experiment in man was undertaken during an epidemic at a military school at La Fleche (Sarthe) in April, 1922[1] Of 521 students exposed to infection, 268 received vaccine by mouth and 253 by the subcutaneous route Five new cases developed in the former group and ten in the latter Since this experience the oral method has been used in larger communities and with apparently successful results Recently two investigators[2] in the department of bacteriology of the University of Washington have observed the effect of oral administration on antibody formation Incidentally they confirm previous clinical reports that the oral administration does not lead to the rather severe systemic response which sometimes follows subcutaneous inoculation Using the triple vaccine they found that 88 5 per cent of their subjects developed agglutinins for typhoid and a lesser number for paratyphoid bacilli This is compared to 80 per cent who, according to the literature, develop agglutinins after subcutaneous inoculation and to 90 to 95 per cent who show a positive Widal reaction after suffering from the disease The administration of bile before the vaccine increased the percentage and shortened somewhat the latent period in which agglutinins are developed This interval, the investigators find, is no longer when the oral method is used than it is for the more orthodox method Complement fixations and precipitins were tested in a smaller number of persons and were found to be present more frequently than in the case of subcutaneous inoculation Rather curiously, the administration of bile did not appear to affect the complement fixations, but the numbers are not large enough to make this observation significant These results show a closer similarity in antibody formation to the immunity reaction of typhoid on the part of oral than of subcutaneous administration It must be noted that actual clinical resistance to disease may not correspond accurately with the development of agglutinins or precipitins, indeed, Besredka in his experiments with the rabbit did not find any such correspondence Moreover, a method that has been so well proved as subcutaneous inoculation against typhoid will not be lightly abandoned However, there seems to be a growing mass of evidence that oral administration is effective In cases in which the subcutaneous method has for one reason or another been rejected, oral administration may reasonably be given a trial

Association News

THE PORTLAND SESSION

Cooperating Exhibit on Eye Infections Due to Gonorrhea

Two years ago, the Section on Urology, with the American Social Hygiene Association cooperating, sponsored an exhibit on gonorrhea in the male. Last year, the Section on Obstetrics, Gynecology and Abdominal Surgery, with the same organization cooperating, arranged an exhibit on gonorrhea in the female To complete the emphasis on the subject of gonorrhea, this year the Section on Ophthalmology has arranged for a special exhibit on eye infections due to gonorrhea, cooperating are the National Society for the Prevention of Blindness and the American Social Hygiene Association

The section has appointed a special committee on section exhibit, consisting of Arthur J Bedell, M D, Albany, N Y, Harry S Gradle, M D, Chicago, and Bernard Samuels, M D, New York, with B Franklin Royer, M D, representing the National Society for the Prevention of Blindness and Walter M Brunet, M D, representing the American Social Hygiene Association, who will act as secretary of the committee.

This committee, representing the Section on Ophthalmology and the two cooperating organizations, is preparing an exhibit which will feature the clinical and pathologic evidences of the diseases of the eye acquired from birth infections of gonorrhea or from infections in any period in life Supplementing this topic will be eye infections due to syphilis, congenital and acquired To those who desire to take part in this exhibit, the committee suggests that they limit their material to fundamental and essential points The exhibits of individuals participating in the special exhibit will be open to awards on the same basis as other exhibits

As the date when all applications for the Scientific Exhibit has passed, the Committee on Scientific Exhibit has assigned a block of space for the use of the Committee on Section Exhibit of the Section on Ophthalmology, which will be allotted to the individual participants in the exhibit dealing with eye infections due to gonorrhea may prolapse through the pylorus into the duodenum and produce a similar defect in the barium shadow (fig. 2). Eliason, Pendergrass and Wright[21] have shown that when prolapsing gastric mucosa is accompanied by a prolapsing polyp or new growth two filling defects are produced, one in the bulb by the pedunculated tumor and another in the pylorus by the hypertrophied gastric mucosa. In these cases an important diagnostic point is the absence of the filling defect in a roentgenogram made with the patient in the erect position and the presence of the defect in one made with the patient in the prone position.

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[1] Besredka A. Local Immunization Baltimore Williams & Wilkins Company 1927 p 137

[2] Hoffstadt, R E. and Thompson R. L Immunological Studies of Typhoid Vaccination by Mouth Am J Hyg 9 1 (Jan) 1929

In differentiating a benign tumor from an ulcer, it should be remembered that an ulcer does not produce a central filling defect. The niche produces a constant disturbance in the outline of the bulb and may be associated with an incisura. The usual finding is hyperperistalsis with delay in motility. Adhesions usually produce an irregularity of the outline of the bulb, with fixation, gastric hyperperistalsis and delayed motility.

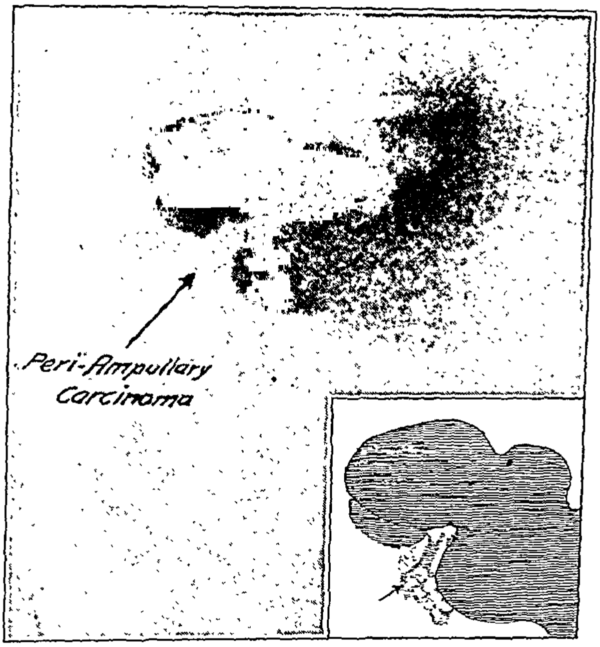

Fig. 19 (case 10).—Carcinoma of the periampullary portion of the duodenum. The stomach was not dilated, and there was active peristalsis. The first portion of the duodenum was obscured by the antrum of the stomach. There were irregularity, narrowing and deformity of the descending portion of the duodenum.

A tumor in the region of the pancreas, pressing on the barium-filled lumen, may produce a central translucency of intraluminal growths, but it is exceptional to have the defect confined to the cap and remain constant in all the horizontal positions (Shiflett [22]).

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[21] Eliason, E. L.; Pendergrass, E. P., and Wright, V. W. M.: Roentgen Ray Diagnosis of Pedunculated Growths and Gastric Mucosa Prolapsing Through the Pylorus, Am. J. Roentgenol. **15**:295, 1926.

Diverticulum of the duodenum is not an exceptionally rare finding. Ritchie and McWhorter [23] collected reports of 76 cases from the literature, and Morrison and Feldman [24] reported 12 personal cases, in 1 of which a carcinoma developed. The best method of recognizing a diverticulum is fluoroscopy, during which the examiner can, by manipulation, cause the pouch to fill and empty. The appearance is characteristic, with regular and smooth outlines. When the ostium of the diverticulum is small, the barium may be retained in a diverticulum for as long as fifty-two days (LeWald [25]). The importance of diverticulum in con-

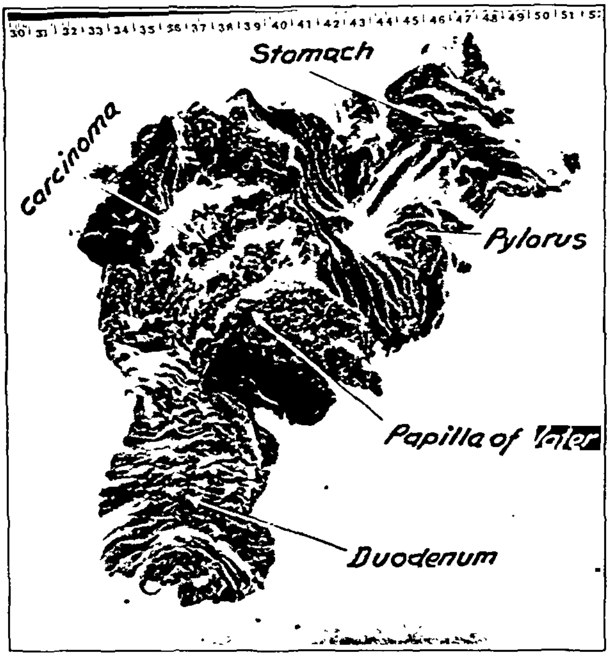

Fig. 20 (case 10).—Photograph of the gross specimen of a carcinoma of the periampullary portion of the duodenum demonstrated in figure 19.

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[22] Shiflett, E. L.: Tumors of the Duodenum and Hypertrophied Gastric Mucosa Prolapsing Through the Pyloric Canal into the Duodenum, Radiology **19**:79, 1932.

[23] Ritchie, H. P., and McWhorter, G. L.: Duodenal Diverticula, Surg., Gynec. & Obst. **25**:485, 1917.

[24] Morrison, T. H., and Feldman, M.: A Case of Carcinoma in a Duodenal Diverticulum with a Consideration of Duodenal Diverticulosis, Ann. Clin. Med. **4**:403 (Nov.) 1925; Autopsy Report of a Case of Primary Carcinoma in a Duodenal Diverticulum, ibid. **5**:326, 1926.

[25] LeWald, L. T.: Right-Sided Diverticulitis and Diverticulosis, Radiology **4**:1 (Jan.) 1925.

nection with carcinoma of the duodenum is twofold: First, carcinoma may arise in a diverticulum (Morrison and Feldman[24]) and, second, the crater of an ulcerated carcinoma may duplicate the roentgenographic appearance of a diverticulum, as occurred in case 12 of our series (figs. 21, 22 and 23).

The difficulties encountered and the errors made in the roentgen examination in cases of cancer of the duodenum are illustrated by the record of this series. Of the 18 cases reported here, roentgenograms of the gastro-intestinal tract were made in 16. The results are shown in table 2. From a study of this it is seen that in the 3 cases in which the lesion was located above the ampulla definite abnormalities were noted. The diagnosis of a malignant growth was made in 1 case and suggested as a possibility in another. In only 1 case was a malignant tumor of the duodenum suspected. The diagnoses were "carcinoma of the pylorus," "obstruction of the duodenum, possibly malignant," and "pyloric obstruction." In 7 of the 9 cases of carcinoma in the periampullary portion of the duodenum, roentgenographic studies of the gastro-intestinal tract were made. The diagnoses were, respectively, "carcinoma of the head of the pancreas," "negative" (2 cases), "per-

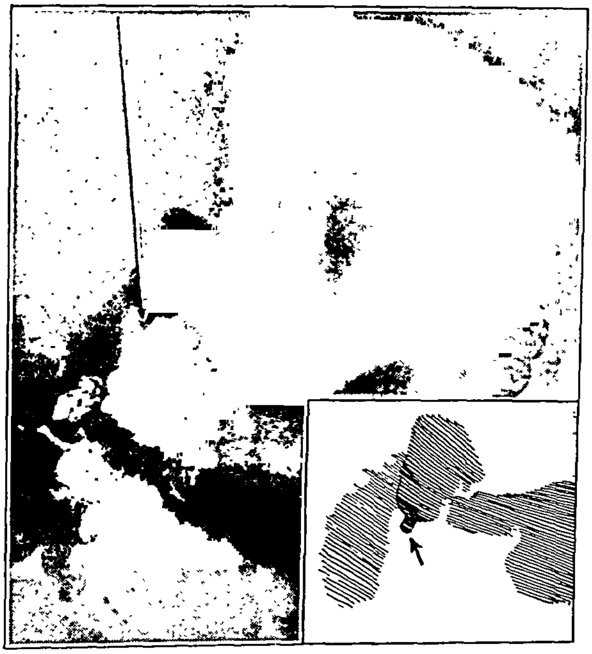

Fig. 21 (case 12).—Carcinoma of the periampullary portion of the duodenum simulating a diverticulum. Note the prominent duodenal bulb and what appears to be a diverticulum of the first portion of the duodenum. At operation this proved to be the crater in an ulcerated carcinoma of the periampullary portion of the duodenum.

forating ulcer," "diverticulum," "obstruction of the second portion of the duodenum" and "biliary obstruction with deformity of duodenum, probably from adhesions." In 6 cases of carcinoma of the infra-ampullary portion the diagnosis was, respectively, "carcinoma of the head of the pancreas," "negative," "duodenal obstruction, probably due to adhesions, but pancreas may be involved" and "deformity and narrowing of duodenum" and (in the 2 remaining cases) "duodenal obstruction."

Here, then, are the diagnoses, made by 6 roentgenologists based on the roentgen examinations in 16 cases in which clinical symptoms were present. In all but 1 of them obvious pathologic changes were evident on the films, yet in only 1 instance was the possibility of a primary carcinoma of the duodenum suggested. In 14 instances, however, the abnormal findings were recognized and described. The conclusions which seem to be justified are: The diagnosis of carcinoma of the duodenum occasionally will be made from the roentgen picture alone, but in most cases a careful correlation and synthesis of the evidence and information derived from all possible methods of clinical investigation are necessary.

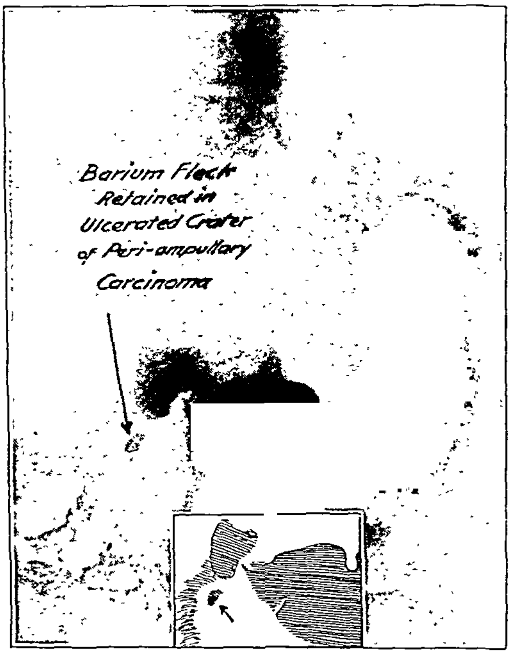

Fig. 22 (case 12).—Roentgenogram of the carcinoma demonstrated in figure 21. Note the barium retained in the crater of the ulcerated carcinoma.

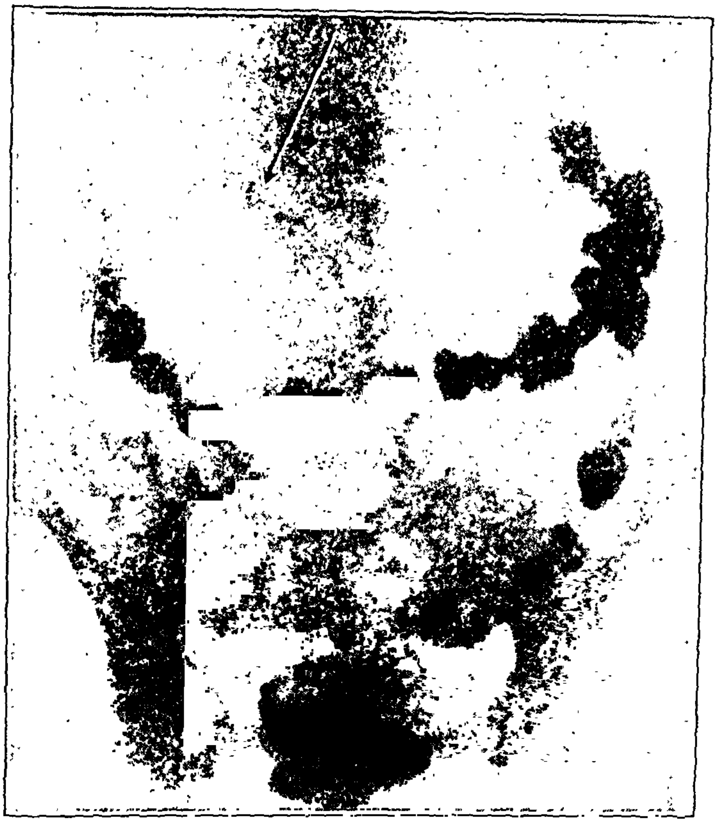

Fig. 23 (case 12).—Roentgenogram of the carcinoma demonstrated in figure 21. Note the barium retained in the crater for twenty-four hours.

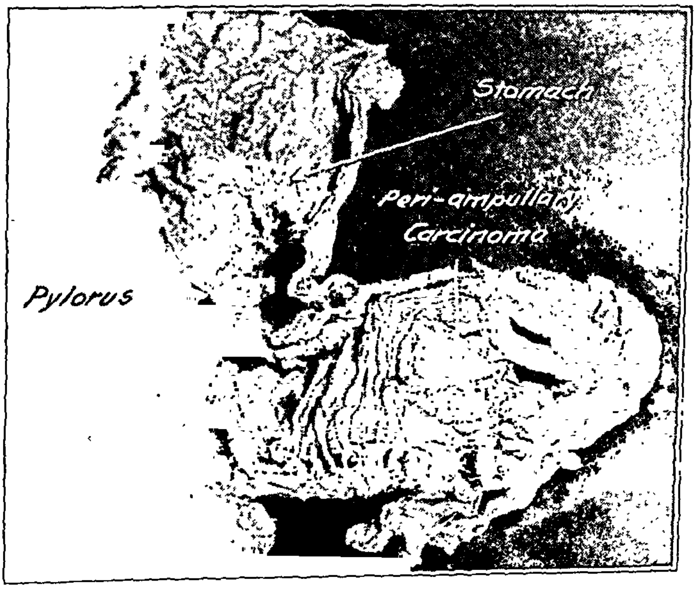

Fig. 24 (case 12).—Gross specimen of the carcinoma shown in figure 21.

DIAGNOSIS

The diagnosis of cancer of the duodenum is attended with so much difficulty that most of the recorded cases were recognized only at operation or at autopsy. In only a few cases reported in the literature has the condition even been suspected. Because of its rarity, it is usually not even considered as a possibility in the differential diagnosis. A further explanation is the fact that cancer of the duodenum is usually mistaken for other lesions of the upper portion of the abdomen. Nevertheless, if the possibility of carcinoma of the duodenum is given

TABLE 2.—*Summary of Roentgen Findings and Diagnosis*

Patient	Location of Growth	Roentgen Findings	Roentgen Diagnosis
M. B.	Supra-ampullary	Dilated pylorus; deformed duodenum distal to cap	Carcinoma of pylorus
D. H.	Infra-ampullary	Deformity of duodenal cap; widening of duodenal loop	Carcinoma of head of pancreas
B. K.	Periampullary	Infiltration of duodenum; gastric retention; enlarged gallbladder	Carcinoma of head of pancreas
C. S.	Periampullary	Hypomotility; large duodenal cap; irregular outline of second portion, partial obstruction of duodenum	No pathologic process
H. S.	Supra-ampullary	Filling defect in junction of first and second portions of duodenum with obstruction and retention	Inclined to think growth benign but must consider possibility of malignancy
L. H.	Supra-ampullary	Almost complete "pyloric obstruction with retention of 90% of barium at 6 hr."	Pyloric obstruction
M. B.	Infra-ampullary	No evidence of cancer or ulcer; no obstruction or dilatation	No evidence of cancer or ulcer in either stomach or duodenal cap; no obstruction or dilatation
H. B.	Infra-ampullary	Obstruction of second and fourth portions of duodenum with gastric retention	Obstruction, probably due to adhesions, but pancreas may be involved
A. B.	Intra-ampullary	Stomach not dilated; active peristalsis; first portion of duodenum obscured by antrum of stomach; irregularity, deformity and narrowing of descending portion of duodenum	No definite diagnosis made
S. A.	Periampullary	Duodenal outline irregular and curves far out to right; 6 hr. retention in stomach; ulcer crater in second portion of duodenum; gallbladder enlarged	Perforating ulcer
J. R.	Infra-ampullary	Obstruction of third portion of duodenum; marked dilatation of entire duodenum and retention of barium	Obstruction of duodenum
W. F.	Infra-ampullary	Obstruction of third portion of duodenum; moderate retention of barium in terminal portion of duodenum; no dilatatoin	No diagnosis made
F. K.	Periampullary	No roentgenograms of gastro-intestinal tract made; injection of biliary tract through gallbladder drain showed dilatation of biliary duct system and obstruction of common duct at ampulla	Dilatation of bile duct
A. B.	Periampullary	Distended gallbladder; irregularity and deformity of second portion of duodenum; no gastric retention	Biliary obstruction; deformity of duodenum probably the result of adhesions
G. B.	Periampullary	Obstruction of second portion of duodenum	Obstruction of second portion of duodenum
C. G.	Periampullary	No evidence of pathologic process in stomach or duodenum (studies made twelve months before admission to hospital)	No evidence of pathologic process in stomach or duodenum

consideration, it should be feasible to make a presumptive diagnosis in certain of these cases. In the early stage, however, symptoms are so few that such a hope is probably not justified, and the diagnosis must await exploratory operation.

The presenting symptoms of cancer of the duodenum usually are epigastric pain and obstruction of the upper part of the intestinal tract, with or without biliary obstruction and jaundice. The logical sequence of procedure, naturally, is to locate the level of the obstruction definitely and finally to determine its cause. The indication that the level of the obstruction is in the stomach, duodenum or upper part of the jejunum

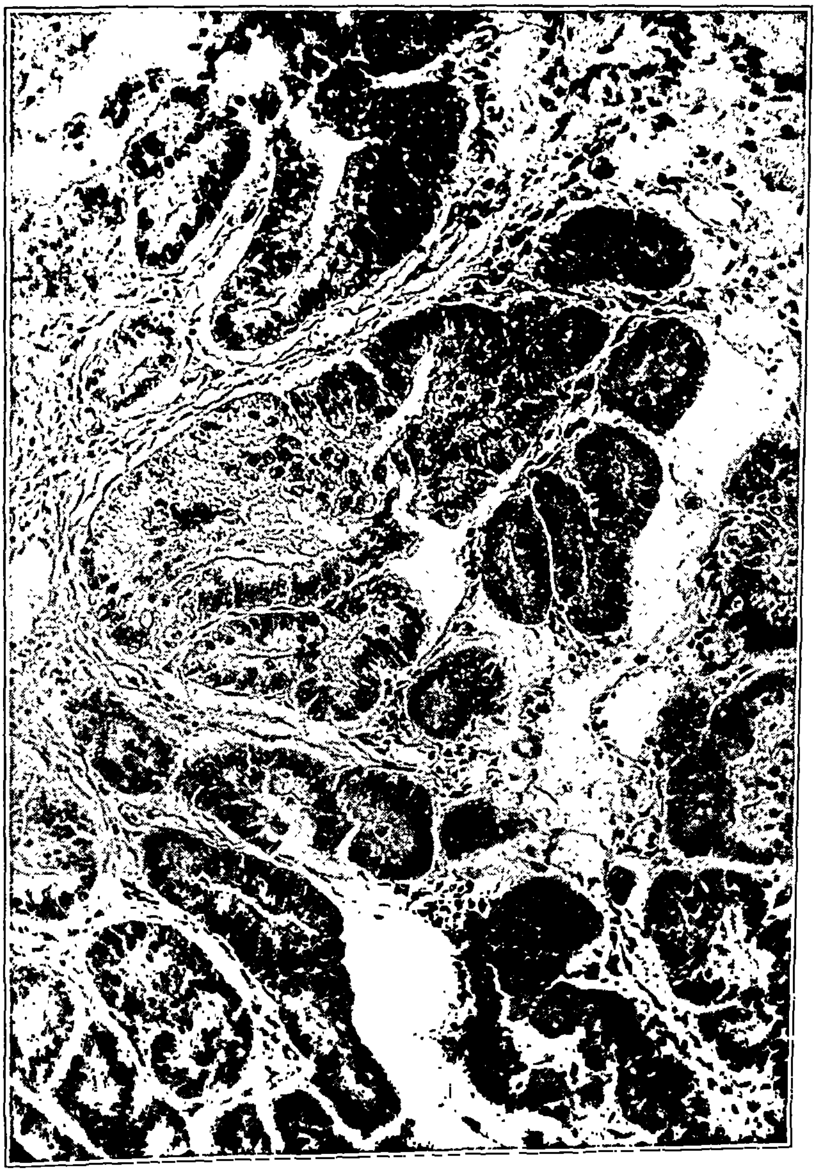

Fig. 25 (case 12).—Microscopic section of the adenocarcinoma shown in figure 21.

is furnished by the presence of gastric retention and dilatation, the absence of intestinal contents in the vomitus and the flat or sunken abdomen without gaseous distention. The commonest obstructive lesion in this region is a carcinoma of the pylorus. This can be ruled out by the roentgen examination revealing a normal gastric outline and motility and a patent or even dilated pylorus. Should the gastric analysis disclose normal free hydrochloric acid, it will help exclude the stomach as the primary site; if diminished or absent, it will not be conclusive.

If bile and pancreatic juice are not found in the vomitus and there is no evidence of jaundice, the point of the obstruction will be in the supra-ampullary portion of the duodenum. The presence of biliary obstruction and jaundice definitely locates the obstruction in the neighborhood of the ampulla, and roentgenograms may show a dilated first portion of the duodenum above an irregular constriction, a gaping pylorus, distended stomach and retention of barium after six hours (figs. 19 and 27). Obstruction of the jejunum can be ruled out by the absence of intestinal contents in the vomitus and by roentgen studies. If the roentgenogram reveals a long, dilated proximal portion of the duodenum above a point of obstruction, with or without irregularity of the duodenal lumen, it is fair to assume that the lesion is in the third portion of the duodenum (fig. 26). When the lesion is below the ampulla of Vater, bile and pancreatic juice are usually found in the gastric contents on repeated examinations, as Mateer and Hartman[18] and others have emphasized.

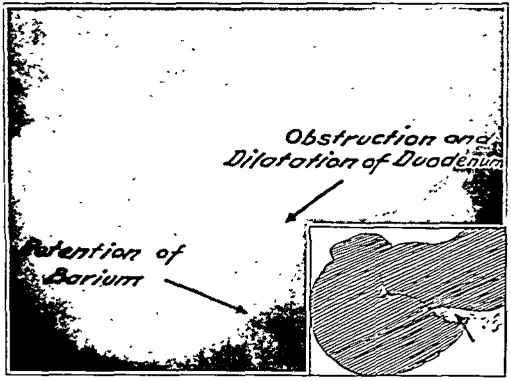

Fig. 26 (case 13).—Obstruction of the third portion of the duodenum with dilatation and retention of barium in the stomach and duodenum after six hours.

Even after the level of obstruction has been determined or assumed, a definite diagnosis of cancer of the duodenum cannot be made until other nonmalignant causes of obstruction have been eliminated. The commonest cause of obstruction of the first portion of the duodenum is constriction by scars of a chronic duodenal ulcer. Evidence against such a cause and in favor of a malignant growth would be the lack of any characteristic history of ulcer, the more rapid development of emaciation, cachexia and stenosis, a marked decrease or absence of free hydrochloric acid, the presence of a palpable tumor and the failure to demonstrate an ulcer by roentgen examination (Eger[16]).

Of all causes of obstruction of the supra-ampullary portion of the duodenum by external pressure mentioned by various authors, enlargement of the gallbladder is, perhaps, the most frequent. Others are: tumors of the omentum, kidney, pancreas and liver, enlarged retroperitoneal glands and an aneurysm of the celiac axis or of the hepatic artery (Fenwick[26]). In differentiating these from cancer of the duodenum, the greatest weight must be given to the following findings, which are common in association with cancer of the duodenum and rare with these other conditions: a severe degree of obstruction of short duration and rapid development, marked cachexia and loss of weight, the presence of blood in the vomitus and stools and marked decrease or absence of free hydrochloric acid in the gastric secretion. Additional aid may be afforded by roentgenographic study of the gallbladder, although it must be remembered that this organ is usually enlarged

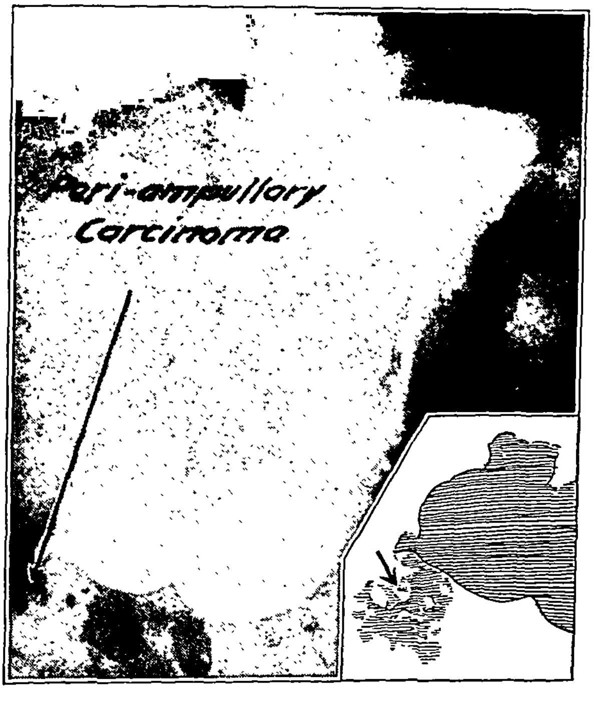

Fig. 27 (case 16).—Carcinoma of the periampullary portion of the duodenum. Note the irregularity and deformity of the second portion of the duodenum.

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[26] Fenwick, W. S.: Primary Carcinoma of the Duodenum, Edinburgh M. J. **10**:309, 1901.

whenever biliary obstruction is produced by a malignant tumor, whether the primary site is the common duct, ampulla, papilla, head of the pancreas or duodenum.

Cancer of the periampullary portion of the duodenum, therefore, is even more difficult to differentiate from obstruction due to other causes. Acute pancreatitis usually has an explosively swift onset, with violent pain and without actual obstruction of the duodenum or alteration in the quantity of free hydrochloric acid in the gastric secretions. Chronic pancreatitis and carcinoma of the head of the pancreas are not likely to cause obstruction of the duodenum or produce blood in the stools or vomitus or cause any reduction in free hydrochloric acid. Cancer of the bile duct, ampulla or papilla causes jaundice of a rapidly progressive unremitting, obstructive type, without symptoms or signs by which it can be differentiated prior to operation or autopsy.

Cancer of the infra-ampullary portion of the duodenum is usually an extensive tumor, often bulky and frequently located immediately proximal to the ligament of Treitz (fig. 26). It, therefore, often may furnish adequate roentgen signs by which the location and extent of the involvement may be fairly well indicated. The differentiation of an obstruction at this level from one in the supra-ampullary portion may be aided by the consistent finding of bile and pancreatic juice in the gastric contents. Other causes of obstruction in the infra-ampullary portion, such as enlargement of the retroperitoneal nodes, retroperitoneal tumor, pressure by superior mesenteric vessels, impaction of a large gallstone in the duodenum and external pressure from a tumor of a contiguous viscus such as the pancreas, must be considered (Eger[16]).

The difficulty of diagnosing cancer of the duodenum is illustrated by the records of this series of 18 cases. Although we have personally examined and studied 5 patients, in only 1 instance was the suggestion made that the lesion might be a primary carcinoma of the duodenum.

TREATMENT

Study of any large series of cases of duodenal carcinoma will reveal two outstanding facts: (1) In a large percentage of cases no evidence of metastasis or local extension of the disease is found at operation, and (2) a high mortality accompanies operative attempts at cure. The first point suggests that successful surgical removal of all the malignant disease might often be feasible if this mortality could be brought down to a reasonable level. The reason for the high mortality is obvious. Not only are the surgical procedures of unusual magnitude, but they must be carried out on patients who often are already moribund from the effects of interference with vital processes. Most of these patients have symptoms of high intestinal obstruction, often complicated by

TABLE 3.—*Summary of Diagnostic Data*

	Origin in Duodenum*	Sex	Age, Years	Duration of Symptoms	Pain in Right Upper Quadrant and Epigastric Distress	Vomiting	Jaundice	Fever and Evidence of Sepsis	Loss of Weight	Palpable Mass in Epigastrium	Palpable Edge of Liver	Occult Blood in Stools	Bile in Stools
Case 1.........	Supra	F.	48	4 mo.	Yes	No	No	No	Yes	Yes, 5 cm., movable	No	No	Yes
Case 2.........	Infra	F.	28	6 mo.	Yes	Yes	No	No	Yes	Yes, 12 cm., fixed	No	—†	—
Case 3.........	Peri	F.	60	3 mo.	Yes	No	No	No	Yes; emaciated	Yes, 10 cm., movable	No	—	—
Case 4.........	Peri	F.	47	2 mo.	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No; clay colored
Case 5.........	Supra	F.	68	9 mo.	Yes	Yes	No	No	Yes; 20 lb.	Yes	Yes	No	Yes
Case 6.........	Supra	F.	70	5 wk.	Yes	Yes	No	Yes	Yes; emaciated	No	No	No —	Yes
Case 7.........	Infra	F.	51	10 mo.	Yes	Yes	Yes	No	Yes; 40 lb.	No	No	..	..
Case 8.........	Peri	F.	52	6 wk.	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Case 9.........	Infra	M.	78	6 mo.	Yes	Yes	No	No	Yes; 25 lb. in 6 wk.	Yes	No	—	—
Case 10........	Infra	M.	71	1 yr.	No	No	No	No	No	No	No	No	No
Case 11........	Peri	M.	18	1 yr.	Yes	No	Yes	No	Yes	Yes; 8 cm. in diameter; moderately movable	No	—	No
Case 12........	Peri	F.	56	2 mo.	Yes	No	Yes	Yes	Yes	Yes; definite mass	No	No	No; pale
Case 13........	Infra	M.	51	2 yr.; gastric distress	Yes	Yes	No	No	30 lb. in 6 wk.	No	...	..	..
Case 14........	Infra	M.	?	......	Yes	...	No	No	Yes	Yes	...	..	..
Case 15........	Peri	F.	36	2 mo.	Yes	Yes	Yes	Yes	Yes; extreme loss	No	Yes	No	No
Case 16........	Peri	M.	58	6 wk.	Yes	No	Yes	Yes	Yes	No	No	No	No; pale
Case 17........	Peri	F.	45	6 wk.	Yes	Yes	No	No	Yes	Yes	No	No	Yes
Case 18........	Peri	F.	45	1 yr.	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No

Bile in Urine	Biliary Drainage, Bile Obtained	Icteric Index	Gastric Analysis	Roentgen Picture with Barium Meal	Course
No	—	—	Normal	Dilated pylorus; deformed duodenum distal to cap	Died 8 days after gastroenterostomy of acute surgical parotitis (bilateral)
No	—	—	—	Deformity of duodenal cap; widened loop	Exploratory laparotomy showed mass thought to be retroperitoneal sarcoma; after 12 roentgen treatments mass regressed; after 6 mo. recurred; radium pack treatments ineffectual; laparotomy and implantation of radon seeds; died 4 days later
No	—	—	—	Pressure defect of greater curvature of stomach; infiltration of duodenum; gastric retention after 6 hours; enlarged liver shadow	Exploratory laparotomy; death from peritonitis
Yes	—	—	—	Dilated first portion of duodenum with irregular outline of second portion and partial obstruction	Rapid downhill course, patient vomiting large amounts of bile-stained fluid; death 33 days later
—	—	—	—	Persistent filling defect of junction of first and second portions of duodenum with obstruction and 48 hours gastric retention	Posterior gastro-enterostomy for cancer of duodenum causing obstruction, involving the first and second parts of duodenum; tumor hard and elastic and obviously malignant; no metastases; no biopsy
—	—	—	—	Almost complete pyloric obstruction with 90% retention at 6 hours	Death 3 days after admission due to myocardial failure
Yes	—	Increased	—	Involvement of duodenojejunal junction by irregular mass causing partial obstruction.	Rapid downhill course; stercoraceous vomiting and death in 3 days
Yes	—	Increased	—	....	Rapid decline; death week after admission
No	—	Normal	—	Obstruction of second and fourth portions of duodenum with gastric retention	Anterior gastro-enterostomy and entero-enterostomy; death 8 days later due to peritonitis
No	—	Normal	—	Dilatation of duodenal cap and first portion; second portion irregularly narrowed and deformed; no diagnosis made	Steady downhill course; death 3 months later
No	—	Increased	Normal	Duodenal outline irregular and curves far out to right; 6 hour retention in stomach; ulcer crater in lower part of second portion of duodenum; gallbladder shadow enlarged	Untraced
No	—	35	—	Shadow of duodenal cap large; second portion narrowed; barium retained in crater in second portion after 24 hours; considered to be diverticulum	Exploratory laparotomy; tumor of second portion of duodenum found and exposed by duodenostomy; distended gallbladder drained by cholecystostomy; death 7 days later due to bronchopneumonia
...	..	.	..	Obstruction of terminal portion of duodenum; dilatation of duodenum; 6 hour retention of barium	Lived 2 years
...	..	.	..	Obstruction of terminal portion of duodenum; small retention; no dilatation	Untraced
Yes	..	100	..	No gastric studies made; dilated bile ducts shown by injection through gallbladder drainage tube	Downhill course; death 4 months after admission
Yes	—	?	—	Irregularity and deformity of second portion of duodenum; gallbladder distended	Exploratory operation; obstruction of common duct; no stone found; T tube inserted; biliary obstruction relieved; hemorrhage from wound 4 weeks later; duodenum exposed and carcinoma excised; death 6 hours later
No	—	—	—	Obstruction of second portion of duodenum with marked dilatation of duodenum and gastric residue	Posterior gastro-enterostomy and cholecystogastrostomy; recovery; lived 2 years
Yes	Slight amount of bile obtained	133	Normal	Negative (12 months before admission)	Steady downhill course for 1 year terminated by massive hemorrhage from duodenal tumor

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* Supra refers to the supra-ampullary portion of the duodenum; infra, to the infra-ampullary portion, and peri, to the peri-ampullary portion.

† The dash indicates that this part of the examination was omitted in this case.

biliary obstruction and chronic hemorrhage. They commonly show advanced degrees of starvation, dehydration, acidosis, anemia, jaundice and gastric distention. A high mortality cannot be avoided if such patients are operated on without adequate preparation.

The dehydration should be corrected by the daily administration of from 3,000 to 5,000 cc. of fluids by all routes. At least from 1,000 to 2,000 cc. of 1 per cent solution of sodium chloride and 10 per cent dextrose should be given intravenously daily. The stomach should be washed out at least once a day. Studies of the blood chemistry will indicate the progress of the patient. The anemia must be corrected by frequent transfusions, preferably of whole blood, which provides ideal nourishment and stimulation to these prostrated patients.

With jaundice present, the danger of hemorrhage increases. Even though jaundice may not be clinically evident, the amount of circulating bilirubin may, nevertheless, increase 800 to 1,000 per cent. The van den Bergh test, determination of the icteric index and estimation of the bleeding and the coagulation time furnish important information. Patients with jaundice should be prepared for operation by restoring the supply of calcium, sodium chloride, water and especially carbohydrates. Walters [27] recommended the administration of 5 cc. of a 10 per cent solution of calcium chloride intravenously for three days; 100 grains (6.5 Gm.) of calcium lactate by mouth daily for four days, and 4,000 cc. of water by all available avenues. In addition, proctoclysis of from 3 to 15 per cent dextrose solution is suggested. A 10 per cent solution of dextrose intravenously is the most direct way of supplying the carbohydrate which is almost a specific for hepatic insufficiency. With such a preparatory regimen, including blood transfusions, Walters [27] was able to reduce the coagulation time from fourteen to two minutes.

OPERATIVE PROCEDURES

The surgical procedures for the treatment of cancer of the duodenum are of two general classes: curative and palliative. In the first group the procedure must be varied according to the location and extent of the growth and the complications which accompany it. Rarely the primary growth may be so small that a simple excision may be sufficient (fig. 3). In the usual case, however, the growth involves so much of the lumen of the duodenum that a resection of the whole segment must be done. If the tumor is in the supra-ampullary portion, well above the bile and pancreatic ducts, this procedure plus posterior gastroenterostomy should be sufficient (fig. 4).

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[27] Walters, Waltman: Obstructive Jaundice: Its Surgical Aspects, Ann. Surg. **93**:1137 (April) 1931.

Carcinoma of the periampullary portion, accompanied by biliary obstruction, entails radical excision of the affected segment, and, if possible, reimplantation of the common bile duct and the duct of Wirsung into the duodenum (fig. 5). When this is done, Cohen and Colp [8] recommended that some operation be done to provide drainage of the gallbladder and thus take the strain off the newly implanted bile duct. The operations which may be employed are choledochostomy, cholecystostomy and cholecystenterostomy. Despite the fact that the addition of this procedure increases the mortality slightly, its advantages deserve consideration. Tension is certainly taken off the suture line, the flow of bile is assured, and should stricture or local recurrence develop, as happened in the cases of Mayo [28] and Rixford,[29] a second operation would not be necessary (Cohen and Colp [8]).

If simple excision of the tumor of the periampullary region (fig. 3) is not sufficiently radical to get beyond the growth, it may be necessary to perform a circular resection of the duodenum, combined with partial pancreatectomy (fig. 4). Cohen and Colp reviewed the literature up to 1927 and found only 4 instances in which the patients had survived this formidable procedure. These were the celebrated cases of Halsted,[28] Kausch,[30] Hirschel [31] and Tenani.[32]

Halsted in 1898 resected a portion of the duodenum, restored its continuity by an end to end anastomosis, reimplanted the bile and pancreatic ducts and established a cholecystostomy stoma. Three months later cholecystoduodenostomy was performed. Kausch did a preliminary cholecystojejunostomy, and two months later resected the duodenum and part of the pancreas and performed pancreaticoduodenostomy and gastro-enterostomy. Tenani, more recently, at his first operation, did an exploratory duodenotomy, followed by posterior gastro-enterostomy, and after dividing the bile duct, he implanted the proximal end into the efferent duodenal segment. He then sutured the duodenum and closed the abdomen without drainage. One month later he resected the second portion of the duodenum and the involved portion of the head of the pancreas. The pancreatic stump was sutured into the efferent duodenal segment (fig. 3).

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28. Cited by Upcott, H.: Tumors of the Ampulla of Vater, with a Report of Two Cases, Ann. Surg. **56**:710, 1912.

29. Rixford, cited by Outerbridge.[14]

30. Kausch, W.: Das Carcinom der Papilla duodeni und seine radikale Entfernung, Beitr. z. klin. Chir. **78**:439, 1912.

31. Hirschel, cited by Pallin, G.: Carcinom des Ductus hepaticocholedochus und seine chirurgische Behandlung (52 schwedische Fälle), Beitr. z. klin. Chir. **121**:84, 1920.

32. Tenani, O.: Surgery of the Papilla of Vater, Policlinico (sez. chir.) **22**: 291, 1922.

Hirschel performed circular resection of the duodenum with end to end suture, choledochoduodenostomy with a tube, resection of a part of the pancreas and pancreaticoduodenostomy and gastro-enterostomy. This extensive procedure was accomplished in the remarkable time of one hour. Since few surgeons could hope to equal this feat, one must agree with Cohen and Colp, from whose paper this material was reviewed, that it would be more practical to perform this operation in two stages, the first of which should be a drainage operation to eliminate the biliary obstruction and thus to get the patient into the proper physical condition to withstand the more exhausting second operation.

The fact that there are only 4 recorded cases in which reimplantation of the head of the pancreas or duct was successfully carried out after resection of the second portion of the duodenum would indicate the extreme hazard of this operation. According to Whipple, Parsons and Mullins,[33] two factors have been responsible for the mortality:

> The first was the mistaken belief that the flow of pancreatic juice is essential to life. This had led surgeons to attempt to reëstablish this flow into the duodenum or jejunum by implanting the resected head of the pancreas or the cut end of the duct into the upper intestine. The activation of the pancreatic ferments by duodenal contents compromised any type of anastomosis in the human subject, especially around the posterior aspect of the duodenum devoid of peritoneum. . . . The second factor was the attempt to carry out the excision of these tumors in one stage. . . .

The technic which they have evolved in their experience with 3 cases of carcinoma of the ampulla embodies the following principles: (1) resection of the descending loop of the duodenum with the pancreas wide of the growth, with no attempt to reestablish the continuity of the duodenum or of the pancreas with the intestine, and (2) division of the operation into two stages. At the first stage, posterior gastro-enterostomy is performed, the common duct is ligated and sectioned below the cystic duct and a cholecystogastrostomy stoma is made in the anterior surface of the stomach, well away from the pylorus, an anastomotic opening at least 2 cm. in diameter being used in order to avoid subsequent stenosis and cholangeitis. At the second stage the descending portion of the duodenum is resected with inversion of the upper and lower ends, and a V-shaped portion of the head of the pancreas is resected together with the common duct. The pancreatic ducts are divided and ligated, and the cut surfaces of the pancreas are carefully approximated. Whipple, Parsons and Mullins have carried out this procedure on 3 patients. The first patient died eight months after the radical operation, following a sequence of events which included stenosis of the cholecystogastrostomy opening, biliary stasis, infection and septicemia. The other 2 patients suffered no disturbance due to lack of pancreatic ferments. The utilization and absorption of fat in both cases were from 85 to 90 per cent, and the patients regained and maintained their normal weight three and seven months after operation.

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[33] Whipple, A. O.; Parsons, W. B., and Mullins, C. R.: Treatment of Carcinoma of the Ampulla of Vater, Ann. Surg. **102**:763, 1935.

Carcinoma of the infra-ampullary portion arises most often close to the duodenojejunal junction. This localization requires resection of the affected segment and reestablishment of the continuity of the intestine by end to end anastomosis or by duodenojejunostomy. End to end anastomosis is often impossible because of the necessity of resecting such a large extent of the duodenum that the ends cannot be approximated (fig. 5). The hazards of this operation are further increased by reason of the edema, hypertrophy and dilatation of the duodenal segment above the obstruction. The marked difference in the caliber of the two segments, the shrinkage of the proximal segment after relief of the obstruction and the strain caused by the rapid peristalsis of this region all increase the danger of leakage at the suture line. In this situation a side to side union, if anatomically feasible, is to be preferred.

In a somewhat analogous situation, Carter[34] resected a carcinoma of the jejunum located 6 inches (15 cm.) below the ligament of Treitz and performed a side to side duodenojejunostomy. He incised the anterior leaf of the transverse mesocolon and swung the distal portion of the jejunum to the right, contraclockwise, to lie beside the terminal portion of the duodenum, which was brought down through a slit in the mesocolon. He then completed a side to side anastomosis (fig. 5). Where so much of the duodenum has been resected that no form of duodenojejunostomy is possible, one must be content with gastro-enterostomy. This procedure, of course, is followed by regurgitation of bile and pancreatic juice into the stomach, and nausea and discomfort may be troublesome unless the stomach is thoroughly washed out daily.

PALLIATIVE OPERATIONS

Palliative operations are distinctly worth while in cases of inoperable cancer. Not only do they prolong life, but they spare the patient the suffering which precedes death by duodenal or biliary obstruction. Patients with inoperable carcinoma of the supra-ampullary portion of the duodenum may be greatly relieved by gastro-enterostomy, with or without an exclusion of the pylorus. Inoperable cancer of the peri-ampullary portion requires gastro-enterostomy and cholecystogastrostomy, cholecystoduodenostomy, cholecystenterostomy or cholecystostomy. Cancer of the infra-ampullary portion, accompanied by obstruction, may require cholecystogastrostomy and gastro-enterostomy.

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[34] Carter, R. F.: Carcinoma of the Jejunum, Ann. Surg. **102:**1019, 1935.

IRRADIATION FOR CANCER OF THE DUODENUM

Irradiation has not played a prominent part in the treatment of duodenal carcinoma. Most of the tumors are of the adult, differentiated type and not likely to respond to any dose of external radiation which can be tolerated by the overlying skin. Rarely an anaplastic tumor is encountered (as in our case 2), which may temporarily respond to external radiation. The literature contains reports of a few cases in which the surgeon at the time of operation placed radium capsules in the end of a duodenal tube introduced into the duodenum by way of the mouth, so as to lie in contact with the lesion for several hours and later be withdrawn. Gold radon seeds have occasionally been inserted into the primary tumor (case 2). None of these procedures have been of much benefit, while the hazards of duodenal fistula, peritonitis and acute pancreatitis are great.

TABLE 4.—*Operative Results*

Patient	Location of Growth	Hospital	Operation	Result
M. B.	Supra-ampullary	Memorial	Posterior gastro-enterostomy	Death due to bilateral surgical parotitis 4 days later
D. H.	Infra-ampullary	Memorial	Exploratory laparotomy and insertion of gold radon seeds	Death 4 days later
B. K.	Periampullary	Memorial	Exploratory laparotomy, duodenotomy and biopsy	Death 11 days later; fecal fistula, peritonitis and bronchopneumonia
S. A.	Periampullary	Post-Graduate	Biopsy, posterior gastro-enterostomy and cholecystogastrostomy	Recovery; patient untraced later
J. R.	Infra-ampullary	Post-Graduate	Gastro-enterostomy	Recovery; patient untraced later
W. F.	Infra-ampullary	Post-Graduate	Jejunostomy	Death 12 days later
G. B.	Infra-ampullary	Post-Graduate	Cholecystogastrostomy and gastro-enterostomy	Recovery; lived 2 yr.
H. S.	Supra-ampullary	Lenox Hill	Posterior gastro-enterostomy	Recovery; patient untraced
A. B.	Periampullary	Lenox Hill	Cholecystostomy, first stage; duodenotomy and excision of tumor at second stage	Death 6 hr. later
H. B.	Infra-ampullary	Polyclinic	Anterior gastro-enterostomy	Leakage at suture line; death due to peritonitis
E. D.	Periampullary	St. John's, Long Island City	Cholecystostomy, duodenotomy and biopsy	Death 3 days later due to bronchopneumonia
F. K.	Periampullary	New Haven, New Haven, Conn.	Cholecystostomy and duodenotomy and biopsy	Recovery; death 14 wk. later

OPERATIVE RESULTS

Operation was performed in 12 of the 18 cases of carcinoma of the duodenum in this series. In only 1 was it possible to attempt to remove the growth. In this instance (case 16) cholecystostomy was performed as a first stage operation. At the second stage, the duodenum was opened, and a small periampullary carcinoma was excised. Death occurred six hours later.

Gold radon seeds were inserted into 1 inoperable tumor (case 2), which had previously undergone marked regression after roentgen therapy. The patient died four days later.

There were 5 postoperative recoveries (41.6 per cent). The location of the tumor and the procedure employed were as follows: (1) carcinoma of the supra-ampullary portion, posterior gastro-enterostomy; (2) carcinoma of the periampullary portion, biopsy, posterior gastro-enterostomy and cholecystogastrostomy; (3) carcinoma of the infra-ampullary portion, gastro-enterostomy; (4) carcinoma of the periampullary portion, cholecystostomy, duodenotomy and biopsy, and carcinoma of the periampullary portion, cholecystogastrostomy and gastro-enterostomy.

There were 7 postoperative deaths (58.3 per cent). The location of the lesion and the operative procedures employed were as follows: (1) carcinoma of the supra-ampullary portion, posterior gastro-enterostomy; (2) carcinoma of the infra-ampullary portion, insertion of gold radon seeds; (3) carcinoma of the periampullary portion, duodenotomy and biopsy; (4) carcinoma of the infra-ampullary portion, anterior gastro-enterostomy; (5) carcinoma of the periampullary portion, cholecystostomy, duodenotomy and biopsy; (6) carcinoma of the periampullary portion, second stage duodenotomy and excision of the growth, and (7) carcinoma of the infra-ampullary portion, jejunostomy.

In 4 instances the duodenum was opened. Specimens for biopsy were taken in 3 instances, and in the fourth case the tumor was excised. Three of these patients died. The causes of death were, respectively, peritonitis, bronchopneumonia and shock.

Of the 5 patients who survived operation, 2 were not traced. One lived fourteen weeks and died at home. The 2 remaining patients (in whom the growth was not removed) lived two years.

SUMMARY

This paper presents a clinical and roentgenographic study of 18 cases of primary carcinoma of the duodenum collected from the material of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, the New York Polyclinic Medical School and Hospital, the New York Post-Graduate Medical School and Hospital, the Lenox Hill Hospital and St. John's Long Island City Hospital, all of New York; the Paterson General Hospital, Paterson, N. J., and the New Haven Hospital, New Haven, Conn. In 5 of the cases the patient was studied during life by us. All were instances of true carcinoma of the duodenal mucosa. Cases of carcinoma of the ampulla or of the papilla of Vater are not included.

The rarity of primary carcinoma is indicated by its incidence of 0.033 per cent of 350,286 autopsies. The sex incidence shows a preponderance of males of 3 : 1.

The usual pathologic type is some form of adenocarcinoma arising from the duodenal mucosa. The gross forms may be scirrhous, bulky and polypoid, or colloid. The pathologic findings in these 18 cases are summarized in table 1.

The symptoms of duodenal carcinoma are chiefly those due to obstruction of the duodenum and neighboring structures. The early stages are featured by anorexia, gaseous eructations, epigastric distention and nausea. As obstruction develops, these become more severe, and pain, vomiting, dehydration, loss of weight and constipation quickly follow. A palpable tumor is found in more than half the cases. The sloughing away of portions of the tumor may temporarily relieve the obstruction or give rise to severe hemorrhage. When the bile passages are obstructed, jaundice of a constant, unremitting type develops. The progress of the disease is swift, and the loss of weight may be extreme.

The average duration of life is about seven months after the onset of symptoms. The shortest duration of life is found in cases in which the lesion is around the ampulla; the longest duration, in those in which the lesion is in the first portion of the duodenum.

In almost every case of duodenal carcinoma which is studied roentgenographically definite pathologic changes can be demonstrated. Such evidence was present on the films in 15 cases in which such studies were made. In 14 of these the pathologic process was recognized and described. In only 1 instance, however, was the possibility of a primary carcinoma of the duodenum suggested. The various roentgenographic findings are described at length and summarized in table 2.

The diagnosis and differential diagnosis are discussed in detail.

The treatment of primary carcinoma of the duodenum is preeminently surgical. The operative mortality is high. In a large percentage of cases at operation there is no evidence of metastasis or local extension of the disease. The surgical removal of all of the malignant tissue might therefore often be feasible if this mortality could be brought down to a reasonable level by efforts to combat the effects of the intestinal and biliary obstructions prior to operation. The patients show advanced degrees of starvation, dehydration, alkalosis, anemia, jaundice and gastric distention. Measures recommended in the preparation of the patient for operation are the restoration of body fluids, mineral salts, carbohydrates and blood supply. Various surgical procedures which have been employed are described, discussed and illustrated. The operative results obtained in the various procedures employed in 12 of this series of 18 cases are described and summarized.

REPORT OF CASES

Case 1.—M. B., a woman aged 48, was admitted to the Memorial Hospital complaining of epigastric pain radiating to the back. The pain was of four months' duration and was severe and cramplike. It was intensified or precipitated by the taking of food, but was not relieved by alkalis and was not accompanied by vomiting. The patient's appetite was good, but she feared to eat because of the pain thus initiated. Loss in weight was moderate but progressive. Physical examination revealed an emaciated woman of 48. The abdomen was sunken, and a hard, smooth, movable mass 5 cm. in diameter could be palpated in the midline immediately above the umbilicus. The liver was not palpable. Roentgenographic and fluoroscopic examination of the gastro-intestinal tract revealed a constant widening of the pyloric sphincter and irregularity in the outline of its surfaces. The duodenal cap was small and slightly deformed but fairly well filled. Beyond the cap there was some irregularity in the outline and distribution of the barium sulfate in the lumen, but the remaining portions appeared normal (fig. 6). Peristalsis was active; there was little delay in the passage of the barium, and no gastric retention was present after six hours. The constant widening of the pylorus was interpreted as suggestive of an annular carcinoma or a fibrotic process as the result of an old pyloric ulcer. Gastric analysis showed normal amounts of free hydrochloric acid. A clinical diagnosis of carcinoma of the pylorus was made. At operation a tumor 5 by 4 by 4 cm. was found involving the posterior wall of the duodenum immediately distal to the pylorus. The tumor had invaded the pancreas, rendering its removal impossible. Posterior gastro-enterostomy was performed, and the abdomen was closed. Four days after operation bilateral parotitis developed, and the swellings became so great that they compressed the pharynx and caused extreme dysphagia and dyspnea. The respiratory difficulty was relieved by an emergency tracheotomy, but death occurred two hours later.

At autopsy a hard ulcerated mass 5 by 4 by 4 cm. was found in the first portion of the duodenum 2 cm. below the pylorus. Metastatic masses were found in the mesenteric nodes of the duodenum, transverse colon and rectum. The liver was not involved. Microscopic examination of the duodenal tumor revealed a malignant adenoma.

Case 2.—D. H., a woman aged 28, had attacks of severe epigastric pain in August 1929. These were accompanied by nausea and vomiting; during the next two months there was marked loss of weight and strength. Her physician discovered an oval mass in the upper part of the abdomen slightly to the left of the midline. An exploratory laparotomy at the Brownsville and East New York Hospital in December 1929 disclosed a mass the size of an orange at the duodenojejunal angle, apparently retroperitoneal in location. No specimen was taken for biopsy. A clinical diagnosis of retroperitoneal lymphosarcoma was made. Immediately after convalescence the patient received twelve treatments by high voltage roentgen therapy. This was followed by the complete disappearance of the abdominal tumor; she gained 20 pounds (9 Kg.) and was restored to her former strength. All symptoms disappeared temporarily, but six months later the tumor recurred and soon reached the size of a grapefruit. Recourse again was had to roentgen therapy, but the tumor did not respond. Symptoms increased in severity, and the patient was referred to the Memorial Hospital. Roentgenograms of the gastrointestinal tract showed no deformity of the duodenal cap or retention of barium after six hours. The curving loop made by the course of the duodenum, however, was greatly widened as though the expansive growth of a tumor in that location had thrust the duodenum aside (fig. 7). A diagnosis of retroperitoneal sarcoma or carcinoma of the head of the pancreas was made, and an exploratory laparotomy was performed by Dr. Frank E. Adair. A rounded, globular tumor mass containing several cystic areas was found apparently retroperitoneally beneath the duodenum and the jejunum. It was impossible to remove the mass, and an attempt was therefore made to accomplish its destruction with interstitial radiation. Twenty-two gold radon seeds containing 55.51 millicuries of radon were inserted into the mass and spaced 1 cm. apart. The patient's condition postoperatively was poor, and death occurred four days later. At autopsy a mass of cancerous tissue was found completely surrounding the duodenum and causing partial constriction. The tumor tissue was white, opaque and partly necrotic as a result of the irradiation. Its texture suggested lymphosarcoma. The mesenteric nodes and the liver were not involved. The stomach was greatly dilated. Microscopic study showed a primary anaplastic adenocarcinoma of the duodenum (fig. 8).

CASE 3.—B. K., a woman aged 60, presented a history of "stomach trouble" for the past five years. Four months before she came to the Memorial Hospital there developed pain in the right upper quadrant, anorexia, loss of weight and moderate constipation. Roentgenograms made elsewhere and not available for study were said to have shown carcinoma of the hepatic flexure of the colon. At this time the patient noted marked feeling of distention after eating. Physical examination disclosed the following abnormal findings: emaciation, dehydration, anemia, edema of the extremities and a slightly movable, irregular, nontender mass the size of an orange in the region of the right kidney. Urologic studies showed diminished function of the right kidney, with many pus cells in the urine. A pyelogram showed changes interpreted as a destructive process in the right kidney, probably inflammatory in nature. A roentgenographic study of the gastro-intestinal tract disclosed a filling defect in the prepyloric segment of the stomach and evidence of upward displacement of the duodenum, pressure on the greater curvature of the gastric antrum, with filling defects in the stomach and duodenum. Some evidence of infiltration of the pylorus and in the descending portion of the duodenum was noted. There was marked retention after six hours (fig. 9). These findings were interpreted as possibly being caused by a tumor of the head of the pancreas. Exploratory laparotomy revealed a large mass 6 by 4 cm. in diameter adherent to the posterior surface of the stomach, apparently arising from the duodenum and impossible to remove. The duodenum was opened, a biopsy specimen was removed, and the duodenum was closed with silk sutures. The abdomen was closed; on the sixth postoperative day bronchopneumonia developed, and the patient died five days later.

Autopsy disclosed focal and pelvic peritonitis as the results of a breakdown of the suture line in the duodenum, a fecal fistula and bronchopneumonia. Surrounding the ampulla of Vater and extending for 6 cm. along the lumen and partly obstructing it, was an annular, polypoid primary carcinoma of the duodenum. There was no evidence of metastases. Microscopic study showed primary malignant adenoma of the duodenum (fig. 11).

CASE 4.—C. S., a woman aged 47, was admitted to the Memorial Hospital on Feb. 17, 1931, with the complaint of weakness, loss of weight, fatigue, nausea and vomiting. These symptoms had arisen four months before and had steadily become more marked. The vomiting appeared to have no relation to meals, and the vomitus usually contained bile. There had been no jaundice until a few weeks prior to admission, when a transitory attack occurred, accompanied by fever. During the past twelve years there had been many attacks of pyuria. Examination disclosed a middle-aged woman in fair general condition. In the right upper quadrant of the abdomen a mass was palpable which appeared to be an enlarged right kidney. A pyelogram showed hydronephrosis of the right kidney. On February 28 the right kidney was removed by Dr. Benjamin Barringer. The specimen contained a broken-down hypernephroma measuring 8 by 7 by 5 cm., the bulk of which showed gross caseous necrosis. The renal pelvis was dilated at the lower pole, where there was marked hydronephrosis. The microscopic diagnosis was "papillary adenocarcinoma of the renal tubule type, with clear and granular cells." The patient made a smooth recovery and felt moderately better for about six weeks, after which there was a return of weakness, nausea and vomiting. She lost weight rapidly, and in June 1931, four months after operation, increasing jaundice, anemia and fever developed. Vomiting of bile-stained fluid became more frequent. She received a transfusion of blood, and for a time improved in general health. Late in July her temperature rose daily to 104 F., accompanied by chills and a steadily increasing jaundice. The stools became clay colored and offensive. Vomiting occurred several times a day, and the vomitus often contained clots of blood as well as coffee-ground material. When readmitted to the Memorial Hospital at this time she was profoundly ill and deeply jaundiced and had lost a great deal of weight. She complained of a dull pain in the epigastrium, which was relieved only by vomiting. The urine was highly colored with bile and hemoglobin. The temperature during the chills rose to 105 F. and occasionally to 106 F. The patient was greatly dehydrated and appeared to be moribund. Large amounts of fluids and dextrose were administered intravenously. The blood count on admission showed 1,550,000 red cells, 14,400 white cells and a hemoglobin content of 40 per cent. The differential count showed 91 per cent polymorphonuclear leukocytes. Three transfusions of a total of 1,950 cc. of whole blood were given within forty-eight hours after admission. The stomach was greatly dilated, and large quantities of blood-stained fluid were removed by gastric lavage. This fluid contained identifiable patches of desquamated gastric mucosa. An attempt at duodenal drainage failed to demonstrate evidence of the patency of the common bile duct. The patient's condition was extremely poor. Vomiting of bright red blood occurred on two occasions, after which the patient grew rapidly weaker and died. No definite diagnosis was made prior to death, although the general picture appeared to indicate a high degree of biliary obstruction and infection. The most likely cause for this was thought to have been a recurrence of the hypernephroma of the right kidney. Roentgenograms made several weeks prior to the last admission showed hypomotility, a large duodenal cap and an irregular outline of the second portion, indicating partial duodenal obstruction.

Autopsy revealed an extreme degree of jaundice; the liver was normal in size, dark green and markedly congested. The gallbladder, common bile duct and hepatic ducts were greatly dilated. One could readily pass a finger down the common bile duct to the ampulla of Vater, which was obstructed by a mass within the duodenum. The stomach was distended to three times its normal size, and the pylorus was widely dilated (fig. 14). The first portion of the duodenum was similarly widely distended. Ten centimeters from the pylorus there was a large, papillary, ulcerated growth involving the entire circumference of the duodenum and extending along the lumen for a distance of 6 cm. This tumor surrounded the ampulla of Vater and completely obstructed it, so that the common duct and the remainder of the biliary system were greatly dilated. There was no evidence of any metastases anywhere in the body and no evidence of any recurrence of the previous hypernephroma of the right kidney. Microscopic study of the tumor of the duodenum showed a primary malignant adenoma (fig. 9). Comparison of the duodenal tumor with the mass previously removed with the right kidney (fig. 12) showed them to be two histologically distinct tumors, and it was the opinion of Drs. Ewing and Stewart that this was a proved example of multiple primary malignant growth.

Case 5.—H. S., a white German woman aged 68, was admitted to the Lenox Hill Hospital on Nov. 4, 1932, complaining of pain in the epigastrium, vomiting, loss of 20 pounds (9 Kg.) in weight and increasing weakness. Symptoms were of three months' duration. On one occasion eight months prior to admission and five months before the onset of symptoms she noted bright red blood in the stools. Examination showed a thin, pale elderly woman, who had evidently lost considerable weight. The edge of the liver was barely palpable. There was a slightly palpable tender mass in the midepigastrium. The stomach was dilated, and an audible splash could be demonstrated. A roentgenographic study of the gastro-intestinal tract disclosed a persistent filling defect in the duodenum at the junction of the first and the second portion. The duodenal wall was markedly rigid, and the filling defect was persistent and caused considerable obstruction, so that at the forty-eighth hour considerable barium was retained within the stomach. The report made by Drs. William H. Stewart and H. E. Illick suggested the possibility of malignant obstruction of the duodenum. On November 9 the abdomen was explored by Dr. Herman Fischer, who found the stomach to be greatly dilated and its walls markedly hypertrophied. The pyloric ring was normal. Beginning on the distal side of the ring and involving the first and second portions of the duodenum was a hard, elastic, whitish tumor tissue which Dr. Fischer considered unquestionably malignant and not inflammatory. There was no evidence of metastases or local extension. A posterior gastro-enterostomy was performed. No biopsy was made. The postoperative course was smooth, and the patient left the hospital in relatively good condition. Two years later reexamination showed the gastro-enterostomy stoma functioning well. There was a constant rounded shadow present which deformed the duodenum and prepyloric area of the stomach. This was considered to be the greatly increased size of the mass found at operation.

Case 6.—L. H., a 70 year old German woman, was admitted to the Lenox Hill Hospital to the service of Dr. Carl Theobald in December 1930, complaining of persistent vomiting and a viselike pain around the upper portion of the abdomen and epigastrium of five weeks' duration. This pain usually subsided after the stomach had been emptied by vomiting. The patient had never been jaundiced. Examination revealed an elderly, emaciated woman in poor physical condition. The stomach was greatly distended, as indicated by marked tympany over most of the abdomen. The diagnosis on admission was obstruction of the pylorus of unknown etiology. After the administration of large amounts of fluids and stimulants, the stomach was emptied by lavage. A roentgenographic study of the gastro-intestinal tract revealed a high grade pyloric obstruction, so that at the sixth hour only 10 per cent of the barium had passed out of the stomach. The character of the obstruction could not be determined from the roentgenograms, although a malignant growth and ulcer were suggested as the most likely causes. Three days later the patient suddenly became weaker and cyanosed, the temperature remained elevated, the pulse grew feeble and she died, apparently of a terminal myocardial failure.

At autopsy the gallbladder was found adherent to the duodenum and communicating with it through a spontaneous cholecystoduodenostomy opening. The stomach was greatly dilated, with thickening of the wall in the pyloric region. The first portion of the duodenum immediately distal to the pylorus was obstructed by an ulcer with a raised necrotic border and base. The surrounding area was indurated and infiltrated. There were no evidences of metastases. The lumen of the small intestine was filled with a large amount of red blood.

Microscopic examination of the ulcerated tumor of the duodenum disclosed adenocarcinoma containing a few areas of anaplastic squamous carcinoma. This case was briefly referred to by Sauer [35] in a discussion of the possibility of carcinoma of the duodenum arising on the basis of a previous duodenal ulcer.

CASE 7.—M. B., a French woman aged 51, was admitted to the Lenox Hill Hospital on Aug. 28, 1930, complaining of loss of weight, weakness, nausea and vomiting of three months' duration. At the time of admission she had lost 40 pounds (18 Kg.) in weight, and the attacks of vomiting occurred several times a day precipitated by the taking of any food or drink. Examination disclosed an obese white woman whose skin was a muddy yellow. She was drowsy, weak and dehydrated because of severe vomiting. Study of the blood chemistry revealed a marked increase in all constituents, probably due to dehydration. The carbon dioxide-combining power was 73.9. Examination of the gastro-intestinal tract revealed no changes recognizable as cancer or ulcer. There was no roentgenographic indication of obstruction anywhere. The patient's condition became steadily worse despite all efforts, and she died six days after admission.

At autopsy the stomach was greatly dilated with gas. In the left upper quadrant of the abdomen was a tumor involving the distal portion of the duodenum and the proximal portion of the jejunum, which was bound down tightly to the splenic flexure and to the transverse colon. The lumen of the duodenum was almost completely occluded by a polypoid tumor, which was extensively ulcerated. This tumor was soft and invaded the duodenal wall in many areas and formed nodules on its outer surface. It encircled the entire duodenum and measured 11 cm. on its long axis. There was no involvement of the liver, nodes or any other structures.

Microscopic study of the tumor showed a small cell adenocarcinoma with extensive areas of spontaneous necrosis.

CASE 8.—C. A., a housewife aged 52, entered the New York Polyclinic Medical School and Hospital on Feb. 18, 1932, complaining of jaundice and pain in the epigastrium. Six weeks previously she noted that her skin and conjunctivae were yellow. Three days later she experienced pain in the right upper quadrant, which she described as "feeling like a dead weight." Soon afterward she had attacks of nausea and vomiting. For the past three months she had a distaste for fats and lost weight and strength. The stools were bloody; constipation steadily increased. The patient was treated by administration of fluids and dextrose and other supportive measures but died one week after admission. Because of her moribund condition no roentgen studies were made of the gastro-intestinal tract except for films of the gallbladder, which were unsatisfactory for diagnosis because of respiratory movements.

Autopsy, performed by Dr. Aaron S. Price, disclosed a jaundiced, emaciated woman. The stomach was enormously dilated. The gallbladder was dilated to a diameter of 8 cm. Arising in the periampullary portion of the duodenum was a carcinoma which had obstructed the ampulla and had secondarily invaded the pancreas. Microscopic study of the tumor showed malignant adenoma and adenocarcinoma, partly diffuse, arising from mucous glands with tendencies toward squamous metaplasia (fig. 18).

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[35] Sauer, P. K.: Carcinoma Following Gastric and Duodenal Ulcer, Ann. Surg. **102**:295, 1935.

CASE 9.—H. B., a man 78 years old, was admitted to the New York Polyclinic Medical School and Hospital on Feb. 23, 1931, complaining of pain in the epigastrium, loss of weight, nausea and vomiting after taking food. The vomitus was greenish and copious, and vomiting was followed by marked symptomatic relief. These symptoms were of six weeks' duration, during which time he had lost 25 pounds (11 Kg.) in weight. Constipation was of long standing. Physical examination disclosed an elderly man, chronically ill, disoriented, dehydrated and feeble. An irregular mass was palpable in the epigastrium. The stomach was greatly dilated and was boldly outlined through the abdominal wall. The intern made a note that despite negative roentgenograms said to have been made elsewhere prior to admission, he believed that the patient had an obstruction somewhere in the duodenum, either from a new growth or from adhesions. A serial roentgenographic study of the gastro-intestinal tract showed "gastric retention due to obstruction of the duodenum, probably caused by adhesions of the second and fourth portions. Involvement of the pancreas should be suspected. The changes found may be due to pancreatitis, ulcer of the duodenum, or tuberculous infection of the peritoneum." The patient was in extremely poor condition. After great efforts to get him in condition for operation by administration of dextrose and fluids by all routes, a laparotomy was done by Dr. Robert E. Brennan with the patient under spinal anesthesia, and an anterior gastro-enterostomy with entero-enterostomy was performed. The patient died several days later.

Autopsy, performed by Dr. Aaron S. Price, disclosed diffuse peritonitis apparently arising from the region of the gastro-enterostomy. The intestine was semigangrenous, with no attempt at healing. In the terminal portion of the duodenum, just above the duodenojejunal junction, was a hard white tumor which had ulcerated and encircled the lumen to produce almost total obstruction. The proximal portion of the duodenum and the stomach were dilated. There was no evidence of local extension or metastases. Microscopic study showed adenocarcinoma arising from cells of the glands of Lieberkühn.

CASE 10.—A. B., a man aged 71, entered the Paterson General Hospital complaining of dizzy spells, sudden transitory attacks of unconsciousness, a feeling of constriction in the esophagus and frequent attacks of dyspepsia with gaseous eructations. There was no history of vomiting or of gross blood in the stools. During the past several months there had been some progressive enlargement of the abdomen. Examination revealed a large indirect inguinal hernia and a hydrocele on the right side and moderate abdominal ascites. No operation was performed except paracentesis. Examination of the stools showed the presence of blood. Roentgenographic studies of the gastro-intestinal tract made after the administration of barium showed that the stomach was not dilated and that peristalsis was active. The first portion of the duodenum was obscured by the antrum of the stomach. The second portion was irregularly deformed and narrowed. No definite diagnosis was made. Permission for exploratory laparotomy was refused. Three months later the patient died.

Autopsy disclosed a broad, annular, papillary and infiltrating carcinoma, 8 cm. in diameter, completely encircling the lumen of the duodenum, arising at a point 1 cm. below the papilla of Vater. The mass was ulcerated and firm and had a border 3 cm. in thickness. There were miliary metastases to the visceral and parietal peritoneum, liver and lymph nodes. Microscopic study showed adenocarcinoma of the duodenum, grade 2. (Dr. William Wuester and Dr. A. Hobson Davis of the Paterson General Hospital permitted us to report this case.)

Case 11.—S. A., an Italian youth 18 years of age, was admitted to the New York Post-Graduate Medical School and Hospital on March 2, 1915, complaining of pain in the epigastrium, loss of weight and a mass in the epigastrium. The first symptom of epigastric pain developed one year prior to admission and was consistently aggravated by eating. Physical examination revealed a fairly well nourished, anemic youth. There was no jaundice. In the epigastrium, slightly to the right of the midline, a hard mass about 5 cm. in diameter could be palpated. The mass was slightly movable, particularly with respiration. The liver was not enlarged, although an enlarged gallbladder could be palpated close to the hard mass already described. Four weeks after admission the skin and conjunctivae showed jaundice, which within two weeks increased markedly. The stools became pale and the urine was dark with bile. A roentgenogram of the region of the gallbladder showed a shadow of an enlarged viscus but no stone. A serial roentgenographic study of the gastro-intestinal tract showed irregularity of the second portion of the duodenum, which curved far out to the right. In the middle of the first portion of the duodenum there was noted a persistent fleck of bismuth, which was still present six hours later. At this time there was a small gastric residue. The findings were interpreted as a perforating ulcer of the inferior horizontal portion of the duodenum. On March 23 the abdomen was explored by Dr. John Erdmann, who found a tumor, 8 cm. in diameter, in the second part of the duodenum, surrounding the ampulla of Vater. A large piece of the tumor was excised for biopsy, and posterior gastro-enterostomy and cholecystogastrostomy were performed. There was no evidence of extension or metastases at operation. The postoperative course was smooth, and the patient was discharged from the hospital much improved three weeks later. He never returned for examination and remained untraced. Pathologic examination of the biopsy specimen showed a smooth, lobulated mass, measuring 4 by 3 by 2 cm. Microscopic study showed a fairly aggressive adenocarcinoma growing in disorderly fashion in a fibrous stroma.

Case 12.—E. D., a woman aged 56, was admitted to St. John's Long Island City Hospital on March 6, 1935, under the care of Dr. Emanuel F. Kalina, complaining of loss of weight, appetite and strength and of chills, fever and jaundice. Two months prior to her illness she began to have pains in the limbs and fever, chills and profuse perspiration. The temperature ranged from 102 to 104 F. The stools became pale, soft or watery, and the skin and conjunctivae became jaundiced. The ingestion of food brought on sour eructations, distention of the epigastrium, nausea and belching of gas, but no vomiting. Examination disclosed jaundice, loss of weight, tenderness in the epigastrium and muscular spasm over the area of the gallbladder. The liver and gallbladder were not palpable. The red cell count was 3,080,000, the white cell count 26,300 and the hemoglobin content, 51 per cent. The icteric index was 35. The van den Bergh direct reaction was positive in thirty seconds. Occult blood was present in the stools. Roentgenograms of the gastro-intestinal tract made after a barium meal showed a normal stomach. The duodenal cap was greatly enlarged, triangular in shape and regular in outline. The descending portion was irregular and narrowed, and barium was retained in the second portion for more than twenty-four hours (figs. 21, 22 and 23). These findings were interpreted as indicating a duodenal diverticulum with partial obstruction. In view of the symptoms of jaundice and fever, indicating biliary obstruction, and the appearance of the duodenum in the films, a diagnosis of possible carcinoma of the head of the pancreas was considered, and exploratory laparotomy was advised. At operation by Dr. William J. Lavelle a markedly distended gallbladder was found. A mass was palpated in the second portion of the duodenum. This was exposed through a small incision and found to be a polypoid carcinoma surrounding the region of the ampulla. The proximal portion of the duodenum was greatly dilated. The duodenal obstruction was partly relieved by freeing adhesive bands in the region of the growth. A portion was excised for biopsy, and the duodenum was closed in two layers. A rubber drainage tube was inserted into the gallbladder and brought out through the incision. Postoperatively, there was profuse drainage of bile from the tube and from a Levine tube introduced into the stomach through the mouth. On the third postoperative day, bronchopneumonia developed, and the patient died four days later.

Autopsy disclosed a friable, polypoid tumor surrounding the region of the papilla but arising in the duodenum (fig. 24). The gallbladder and common duct were dilated. The liver was smooth and green. There was no evidence of local extensions or metastases. The suture line around the opening in the duodenum was intact. Microscopic study of the specimen showed a papillary adenocarcinoma of the duodenum (fig. 25).

Case 13.—J. R., a man aged 51, complained of sour stomach and heartburn of two years' duration, with nausea, vomiting and epigastric pain of eight weeks' duration. Six weeks prior to admission a roentgenographic study of the gastro-intestinal tract revealed retention of barium after six hours. He had lost 30 pounds (13.6 Kg.) in the past six weeks, his weight falling from 171 to 141 pounds (77.6 to 64 Kg.). Physical examination showed a markedly emaciated patient. Urinalysis showed the presence of sugar. Roentgenograms of the gastro-intestinal tract revealed obstruction of the third portion of the duodenum with marked dilatation of the entire duodenum and retention of barium within the stomach and duodenum after six hours (fig. 26). A diagnosis of duodenal obstruction was made. The operation was performed by Dr. John F. Erdmann, on May 25, 1929, and a carcinoma of the terminal portion of the duodenum was found. There were multiple metastases found in the liver. A gastro-enterostomy was done, and the patient was discharged from the hospital nineteen days later. He subsequently was untraced.

Case 14.—W. F., a man aged 45, complained of nausea, vomiting, epigastric pain and distention. Previous examination at another hospital had not yielded a definite diagnosis, and an exploratory laparotomy had been advised. A roentgenographic series of the gastro-intestinal tract showed the terminal portion of the duodenum distinctly outlined by the barium in a manner which suggested some obstruction of the lumen, but this escaped detection at the time and was noted only after the patient had been operated on. Dr. Erdmann's clinical diagnosis was carcinoma of the liver with generalized abdominal carcinomatosis. At operation on Sept. 21, 1927, a definite carcinoma of the terminal portion of the duodenum was found. There was an extensive generalized carcinomatosis involving all the abdominal structures in addition to bulky metastases in the liver. A palliative jejunostomy was performed. The patient failed steadily and died twelve days after operation. Permission for autopsy was not obtained.

Case 15.—F. K., a woman aged 36, was admitted to the New Haven Hospital on April 24, 1935, complaining of weakness, anorexia and a constant dull pain in the right upper quadrant which had been present for two months. A month prior to admission she had an attack of severe pain in the same region, associated with a progressively increasing jaundice. The pain radiated through to the back. The skin became yellow, the stools were pale and clay colored, and the patient lost weight steadily. There was no nausea, vomiting or tarry stools. Physical examination showed marked jaundice, tenderness in the region of the gallbladder, rigidity of the abdominal muscles and enlargement of the liver. The red cell count was 4,200,000, the white cell count 13,600 and the icteric index 100. The van den Bergh test was positive. The stools were negative for occult blood or bile. A diagnosis of chronic cholecystitis and cholelithiasis was made, and on May 5 an exploratory laparotomy revealed a large, tense gallbladder and a mass in the region of the ampulla, which was thought to be an impacted stone. Because of brisk bleeding which occurred, the only procedure attempted was the insertion of a drain into the gallbladder. Twenty-six days later the abdomen was again explored in the service of Dr. S. C. Harvey, and a large friable, cauliflower mass was found surrounding the ampulla of Vater. The duodenum was opened and a biopsy specimen was removed. The postoperative course was stormy, and a fecal fistula developed in the lower angle of the wound. The patient left the hospital in poor condition, became progressively worse and was brought back to the hospital, where she died on September 9.

Autopsy disclosed a markedly emaciated woman weighing only 65 pounds (29 Kg.). There was a fecal fistula leading down to the transverse colon. The stomach was markedly distended to five times normal size and filled nearly the entire abdominal cavity. The proximal duodenum was distended to four times its normal size. The ampulla of Vater was surrounded by a friable, fungating tumor mass 3 cm. in diameter, which occluded the lumen. The lymph nodes of the celiac and peripancreatic regions were enlarged and obviously involved by metastases. The liver was not involved, although the pancreas was directly invaded. Microscopic examination of a specimen from the periampullary tumor showed an adenocarcinoma of high columnar cells.

Case 16.—A. B., a man aged 58, was admitted to the Lenox Hill Hospital, service of Dr. Robert C. Schleussner, with a complaint of attacks of fever lasting only one or two days, accompanied by chills, intermittent jaundice and tenderness in the right upper quadrant. Roentgenograms of the abdomen made without the administration of any dye showed the gallbladder clearly outlined and enlarged. This appearance was interpreted as evidence of chronic cholecystitis. Roentgenograms and fluoroscopy of the gastro-intestinal tract made after the administration of barium revealed no evidence of ulcer or cancer in the stomach or duodenum. The second portion of the duodenum, however, showed some deformity, which was considered to be due to adhesions. There was no gastric residue at six hours. Physical examination disclosed the following positive findings: moderate jaundice, fever and tenderness in the right upper quadrant. The stools did not contain bile; the urine was colored with bile. After a clinical diagnosis of impacted stone in the common duct, exploratory operation was done by Dr. Otto C. Pickhardt, and the common duct found to be obstructed at the ampulla. The dilated duct was explored, but no stone found. Because of the patient's condition it was thought inadvisable to search further for the cause of the obstruction at this stage, and the operation was terminated with the insertion of a T tube into the duct to relieve the biliary obstruction. Postoperatively there was a profuse drainage of bile from the tube, and the jaundice cleared up within a week. The condition of the patient improved slowly. Four weeks after the operation he suddenly vomited a large quantity of bright red blood and simultaneously began to bleed from the abdominal wound. A transfusion of 400 cc. of whole blood was immediately given to the patient. On the following day the wound was opened and large blood clots removed. No source of the bleeding was found. The duodenum was exposed, and a small mass was palpable in the second portion. The duodenum was opened, and a soft, friable tumor mass was found on the posterior surface close to the ampulla. This was excised, and the duodenum was closed. There was no evidence of metastases within the abdomen. Six hours later the patient died. Microscopic examination of the specimen removed from the duodenum showed adenocarcinoma.

Case 17.—G. B., a woman aged 45, complained of epigastric pain, nausea and vomiting. Symptoms had been present for six weeks. A roentgenographic study of the gastro-intestinal tract showed obstruction of the second portion of the duodenum. Operation by Dr. John F. Erdmann disclosed a large tumor mass which had almost completely encircled and obstructed the periampullary portion of the duodenum. The obstruction was relieved by cholecystogastrostomy and posterior gastro-enterostomy. The postoperative course was smooth, and the patient lived for two years and died at home. Permission for autopsy was not obtained.

Case 18.—C. G., a woman aged 45, entered the Lenox Hill Hospital on Feb. 13, 1936, service of Dr. Abraham L. Garbat, complaining of intermittent fever, jaundice, pain in the right upper quadrant, pruritis, loss of weight, weakness, anorexia and vomiting. The symptoms began one year prior to admission and had persisted thereafter, except for four short remissions during that time. Roentgenograms of the gastro-intestinal tract made twelve months before admission showed no definite abnormality of the stomach or duodenum. Physical examination revealed a markedly jaundiced woman in an extremely poor condition because of sepsis, vomiting and dehydration as the consequence of biliary and duodenal obstruction. The urine was dark and contained considerable bile. The stools were clay colored and were negative for tests for bile. The icteric index was 133; the carbon dioxide-combining power was 34 volumes per cent. Analysis of the duodenal contents on seven occasions showed only slight evidence of bile. After the intravenous administration of dextrose in saline solution the patient's condition improved slightly, but two days after admission she suddenly became restless, passed into shock and died.

Autopsy disclosed a markedly jaundiced, emaciated woman about 45 years of age. When the abdomen was opened a massive hemorrhage was found behind the peritoneum, within the peritoneal cavity and inside the lumen of the small intestine. Both pleural cavities contained considerable clear fluid. The liver was dark green and enlarged and extended 5 cm. below the costal margin. The gallbladder had been removed at operation eleven years before. The bile and pancreatic ducts were greatly dilated, the common duct measuring 1.5 cm. in diameter. Surrounding the ampulla of Vater was a raised, polypoid ulcerated tumor, 2.5 cm. in diameter. There was no evidence of metastasis or extension anywhere within the abdomen. Microscopic examination of the duodenal tumor showed adenocarcinoma.

ABSTRACT OF DISCUSSION

Dr. E. V. Powell, Temple, Texas: The paper by Drs. Hoffman and Pack recalls a case that I reported to the New York Roentgen Society while I was at St. Bartholomew's Hospital. It was one of duodenal carcinoma, which I was lucky enough to diagnose as a tumor. It was an adenocarcinoma and gave a filling defect about the size of a golf-ball within the duodenal cap. Obstruction was almost, but not entirely, complete. I have since seen one other carcinoma of the duodenum which arose near the papilla and terminated fatally. In the first case operation was performed and radon seeds were implanted. The patient lived long enough to get away from the hospital, but I do not know what happened to him later.

Dr. Ross Golden, New York: Drs. Hoffman and Pack's unfortunate experience with roentgen diagnosis of carcinoma of the duodenum should be a stimulus to roentgenologists. Carcinoma of the duodenum can be correctly interpreted by roentgen examination.

One of the young men of the hospital, who had only about three or four years' experience in roentgenology, correctly made such an interpretation a few years ago, based on the fact that the mucous membrane of the second portion of the duodenum was destroyed over one side. The mucosal folds of the duodenum below the first portion are marked, making that kind of an interpretation relatively easy.

One must become acutely conscious of the mucous membrane of the gastrointestinal tract. Within a year one of the residents at the hospital with which I am associated demonstrated a duodenum in which the mucous membrane was destroyed from about the beginning of the second portion clear through the second portion into the jejunum. He thought it was probably not a carcinoma and raised the question of a lymphoblastoma. The pathologist called the growth a lymphosarcoma, and the patient has improved under roentgen treatment.

CARE OF THE SEVERELY BURNED

WITH SPECIAL REFERENCE TO SKIN GRAFTING

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From my experience with the care of the severely burned, I believe that the following points are especially important: 1. During the first day or so the systemic changes assume a position of greater importance than the local injury. 2. Later in the care of the local lesion the use of fundamental principles of cleanliness and good drainage, in contradistinction to the use of this and that preparation or technic which ignores these principles, represents sound treatment. 3. Insistence on the necessity of early resurfacing of the resultant granulating surface should be stressed because of the marked decrease in the period of convalescence with its economic potentialities and the extent to which functional incapacitation from contracture or cosmetic blemishes can be forfended. 4. When the time for skin grafting is at hand, dependence on fundamental principles and methods, in contradistinction to the use of unusual types of grafts with or without a "far-fetched" method of placement, puncturing or dressing, usually will tend toward real success.

In a series of 514 skin grafts which were transplanted at 361 separate operations on 257 different persons, 299 of the grafts were transplanted at 193 separate operations on 144 different persons to alleviate the damage resulting from a burn of one type or another. Moreover, for my purpose the damage found either of a potentially deforming or of an actual contractural character in a series of burned persons presents most of the situations necessary to exemplify the principles involved in the successful grafting of skin.

EARLY CARE

In the group of 144 burned persons for whom skin grafting to a granulating surface was eventually necessary, 32 were cared for at one stage or another of a large severe acute burn. Not included in this

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From the Department of Surgery of the University of Kansas School of Medicine.

Read before the Section on Surgery, General and Abdominal, at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 15, 1936.

group are 5 persons, 3 of whom died within from one to three days after the burn and 2 of whom died of complications in the intermediate period before skin grafting could be completed.

Systemic Treatment.—Most of the emphasis in these cases was focused early on the alleviation of the profound systemic disturbance which occurred when the burn was of extensive proportions. In the patients seen immediately after being burned systemic treatment was based on the premise that besides considering an adequate amount of morphine for the alleviation of pain as a sine qua non and attempting to preserve normal body temperature, the salient point in the treatment was the early and more or less continuous replacement by substitution of that which had been lost and was being lost from the "circulatory tree." The work of Underhill and his co-workers[1] and Blalock[2] on the severely burned has served to draw attention to the rapid loss of blood plasma from the circulatory tree in amounts which soon may cause death. The lost plasma apparently tends to accumulate in the tissues adjacent to the area burned, and the mechanism of reabsorption tends to be rather negligible during the first thirty-six to forty-eight hours.

Main reliance for the purpose of dilution and replenishment of the fluids was placed on hypotonic saline solution. To replenish the protein lost from the circulatory fluids, autogenous blood was considered the solution nearest to that of the normal fluid. As a rough index

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1. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns and Their Significant Systemic Treatment, Arch. Int. Med. **32**:31-49 (July) 1923. Underhill, F. P.: The Lethal War Gases, New Haven, Conn., Yale University Press, 1920: The Physiology of Experimental Treatment of Poisoning with the Lethal War Gases, Arch. Int. Med. **23**:753-770 (June) 1919. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Studies on the Mechanism of Water Exchange in the Animal Organism: I. The Nature and Effects of Superficial Burns, Am. J. Physiol. **95**:302-314, 1930; II. Changes in Capillary Permeability Induced by a Superficial Burn, ibid. **95**:315-324, 1930. Underhill, F. P.; Fisk, M. E., and Kapsinow, R.: III. The Extent of Edema Fluid Formation Induced by a Superficial Burn, ibid. **95**:325-329, 1930. Underhill, F. P., and Fisk, M. E.: IV. The Composition of Edema Fluid Resulting from a Superficial Burn, ibid. **95**:330-333, 1930. Underhill, F. P.; Fisk, M. E., and Kapsinow, R.: V. The Relationship of the Blood Chlorides to the Chlorides of Edema Fluid Produced by a Superficial Burn, ibid. **95**:334-338, 1930; VI. The Composition of Tissues Under the Influence of a Superficial Burn, ibid. **95**:339-348, 1930. Underhill, F. P., and Fisk, M. E.: VII. An Investigation of Dehydration Produced by Various Means, ibid. **95**:348-363, 1930; VIII. A Study of Dehydration by Pilocarpine Under Varied Dietary Conditions, ibid. **95**:364-370, 1930.

2. Blalock, Alfred: Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of Low Blood Pressure After Burns, Arch. Surg. **22**:610-619 (April) 1931.

to the amount of solution needed, the extent[3] and severity of the burn were considered in relationship to the size and age of the patient, and by means of periodic determinations of the blood pressure and repeated estimates of the hemoglobin content, the amount of plasma lost and the degree of blood concentration were roughly estimated. In a few instances adults received as much as from 4 to 8 liters of isotonic saline solution per day. The work of Smith and Mendel[4] and of Rowntree[5] on water intoxication indicates the safety of these amounts. Sometimes, if the patient was a child with some evidence of acidosis, a 5 per cent solution of dextrose in amounts to alleviate the symptoms was considered advisable. Repeated transfusions of blood were given according to the probable degree of the loss of plasma. When the oxygen-combining power of the blood was lowered, sodium bicarbonate was given in sufficient quantities to turn the urine alkaline. Ordinarily, after the first forty-eight hours, the systemic treatment simmered down to attention to a relatively high fluid intake and output and general symptomatic care of the patient. For preservation of a normal body temperature, an overhead canopy heated by electric lights was found to be efficient.

Early Local Care.—The early local care of the wound was deemed to be important mainly in a negative way. Usually some type of fixative, such as tannic acid (most frequently), gentian violet, dehydrated alcohol, trinitrophenol or aluminum acetate, was used, but not with the idea of the fixative being of great value in the correction of the disturbance in physiologic relations but because of the cleanliness of the method and the lessened disturbance to the patient.

As Taylor[6] has noted, the too ambitious use of tanning solutions in cases of superficial burns may fix not only the dead layers of skin but any of the germinal layer and the appendages of the skin that may remain, such as the hair follicles or the sebaceous glands. To the fixation method associated with Davidson's name[7] there has been attributed by him and others[8] a decrease in mortality principally during the second twenty-four hour period. In the cases considered in this paper a decrease in mortality during this period seemed to be associated rather closely with the proper systemic management of the patient rather than with the care of the local lesions.

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[3] Berkow (A Method of Estimating the Extensiveness of Lesions [Burns and Scalds], Based on Surface Area Proportions, Arch. Surg. **8**:138 [Jan.] 1924) has again within recent years emphasized that for the purpose of prognosis it is important for the physician to estimate at an early time the relative area of the body surface involved.

[4] Smith, A. H., and Mendel, L. B.: The Adjustment of Blood Volume After Injection of Isotonic Solutions of Varied Compositions, Am. J. Physiol. **53**:323 344, 1920.

[5] Rowntree, L. G.: Water Intoxication, Arch. Int. Med. **32**:157-174 (Aug.) 1923; The Effects on Mammals of the Administration of Excessive Quantities of Water, J. Pharmacol. & Exper. Therap. **29**:135-159, 1926.

[6] Taylor, Frederic: The Misuse of Tannic Acid, J. A. M. A. **106**:1143-1145 (April 4) 1936.

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When proper early precautions were taken the development of a true abscess beneath the tanned crust was of rare occurrence. When a collection of pus did occur, its appearance was noted usually at about the time that the separation of the dead soft tissues from the live tissues was nearing completion, i. e., about the end of the third week. Then a small incision through the crust or even the application of a dressing moistened with saline solution gave adequate drainage.

THE INTERMEDIATE PERIOD

In the series of cases reported here 93 thin grafts were applied to cover a granulating surface. These were applied on 59 patients at 80 separate operative procedures. The granulating areas covered averaged 89.6 sq. cm., and 32 of these were caused by a burn with an average area grafted of 93.6 sq. cm.

Relation of Area and Depth to Contractural Deformity.—The early recognition of not only the depth of epithelial destruction but the area of complete epithelial loss is an essential point that needs to be grasped by the surgeon if he is to develop a practical successful method of repair. In cases of burns of a degree (fig. 1) that destroy only a portion of the epithelial "pegs" within a period of from two to three weeks, reepithelization from below upward and skin grafting were seldom necessary. When all layers of the epithelium had been destroyed, the wounds tended to close by two methods: (1) by fibrosis and contraction of the granulating base and (2) by a slow scarred epithelization progressing centrally from the edges (fig. 2). The anatomy of the part very largely determined the tendency for the surface to close by the first or the second method. Thus, when the denuded area was over the side of the ribs or in the middle of the thigh, where the bony structures were strong and the soft tissues only moderately yielding, a greater part of the closure of a wound was made by the scarred epithelium, which, according to the natural rapidity of epithelial growth, grew in from the circumference. On the other hand, when the destruction of soft tissues was located in front or back of a joint which could be restricted in its normal radius of movement, the greater part of the wound closed by fibrosis, depending somewhat on whether the limiting scar was within or without the angle of movement. The larger the original surface destruction, the greater was the tendency to contracture and limitation of flexion or extension. In some instances an additional factor was added by the density and contractile pull of an innate tendency to the formation of a keloidal scar.

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[7] Davidson, E. C., and Matthew, C. W.: Plasma Proteins in Cutaneous Burns, Arch. Surg. **15**:265-274 (Aug.) 1927.

[8] Davidson, E. C.: The Prevention of the Toxemia of Burns: Treatment by Tannic Acid Solution, Am. J. Surg. **40**:114-116 (May) 1926; Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, Arch. Surg. **13**:263-277 (Aug.) 1926; Tannic Acid in the Treatment of Burns, Surg., Gynec. & Obst. **41**:202-221, 1925. Glover, D. M.: Six Years of Tannic Acid Treatment of Burns, ibid. **54**:798-805, 1932. Harris, R. I., quoted by Davidson, E. C., and Penberthy, G. C.: Treatment of Burns in Children with Tannic Acid, Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America **5**:265-268, 1929. Herzfeld, G.: Treatment of Burns and Scalds by Tannic Acid, Practitioner **122**:106-111, 1929. Wilson, W. C.: The Tannic Acid Treatment of Burns, Medical Research Council, Special Report Series, no. 141, London, His Majesty's Stationery Office, 1929. Beekman, F.: Tannic Acid Treatment of Burns, Arch. Surg. **18**:803-806 (March) 1929. Bancroft, F. W., and Rogers, C. S.: Treatment of Cutaneous Burns, Ann. Surg. **84**:1-18, 1926; Arch. Surg. **16**:979-999 (May) 1928; New England J. Med. **202**:811-822, 1930.

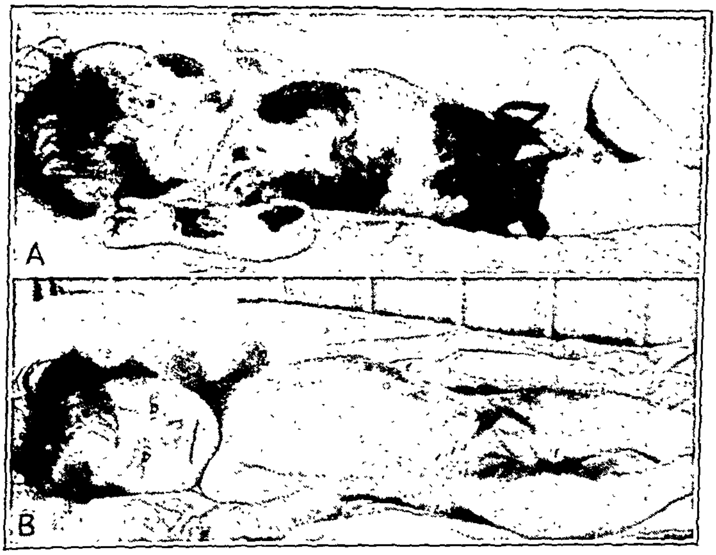

Fig. 1.—*A*, photograph of a rather superficial burn with fixative applied. In only one area (over the pubis) have all the layers of epithelium been destroyed. In a burn of this depth epithelization is quick because the new epithelium springs from the base. *B*, photograph of the same child taken three weeks after the burn.

Preparation for Resurfacing.—By the end of the third week or the early part of the fourth week, when it was deemed that a well developed limiting wall of granulation tissue had formed, an abrupt change was made in the method of handling the local area. At this time the local burned area was wrapped within a wet thick gauze roll (fig. 3 *A*), which was reapplied twice daily and kept continuously wet. Early during this period, but not before, while the wound was being dressed without anesthesia, gross dead tissues sometimes were cut away with scissors or a knife. When some difficulty or pain was experienced in removing the dressing, if the patient's condition permitted, the patient was placed in a tub bath (fig. 3 *B*) for fifteen or twenty minutes until the dressings fell off more or less spontaneously.[9] Too long a period of immersion was found to be weakening in several instances,

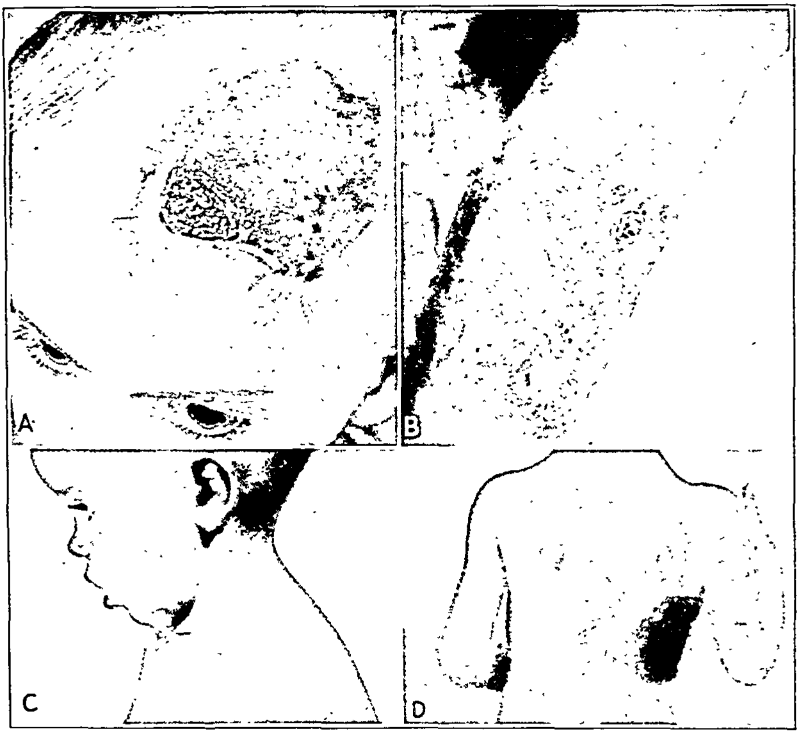

Fig. 2.—*A*, photograph of a burn, which if allowed to scar over without aid will be forced by the underlying anatomy to close principally by epithelization from the circumference. *B*, photograph of a burn, which because of the anatomy of the region has closed principally by epithelization from the circumference. *C*, photograph of a burn which has closed principally by the contracture of the fibrotic base. *D*, photograph of a burn which over the ribs will close principally by epithelization from the circumference and in the axilla principally by contractural fibrosis.

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[9] Paulus of Aegina, 629 to 690 A.D. (cited by Pack, G. T., and Davis, A. H.: Burns: Types, Pathology and Management, Philadelphia, J. B. Lippincott Company, 1930) is said to be the first to use the continuous water bath. Passavant (Bemerkungen über Verbrennungen des menschlichen Körpers und deren Behandlung mit dem permanenten warmen Bade, Deutsche Klin. **10**:348, 365 and 373, 1858) first described and Hebra (Ueber continuirliche allgemeine Bäder und deren Anwendung bei Behandlung von Verbrennungen, Allg. Wien. med. Ztschr. **6**:331 and 359, 1861) popularized the use of a continuous wet dressing.

and if the patient was showing considerable constitutional reaction immersion was not deemed advisable. Immediately after immersion a wet gauze roll was wrapped about the denuded area.

Saline solution was usually used, but at other times a saturated solution of boric acid or of magnesium sulfate was used. The particular solution used, provided it was not toxic, was not considered of great importance. The advantages of wet dressings were judged to be promotion of drainage, maceration at the line of demarcation, mechanical aid to the separation of slough and possibly some mechanical stimulus to the formation of a proper bed of granulation tissue. Moreover, the cleanliness of the method and the repetition of the dressing twice daily were regarded of importance in shortening the period necessary to give a proper granulating bed. Besides the general condition of the patient, the most important aid to early epidermization from the circumference of the wound was cleanliness (fig. 4 *A* and *C*). In the consideration of

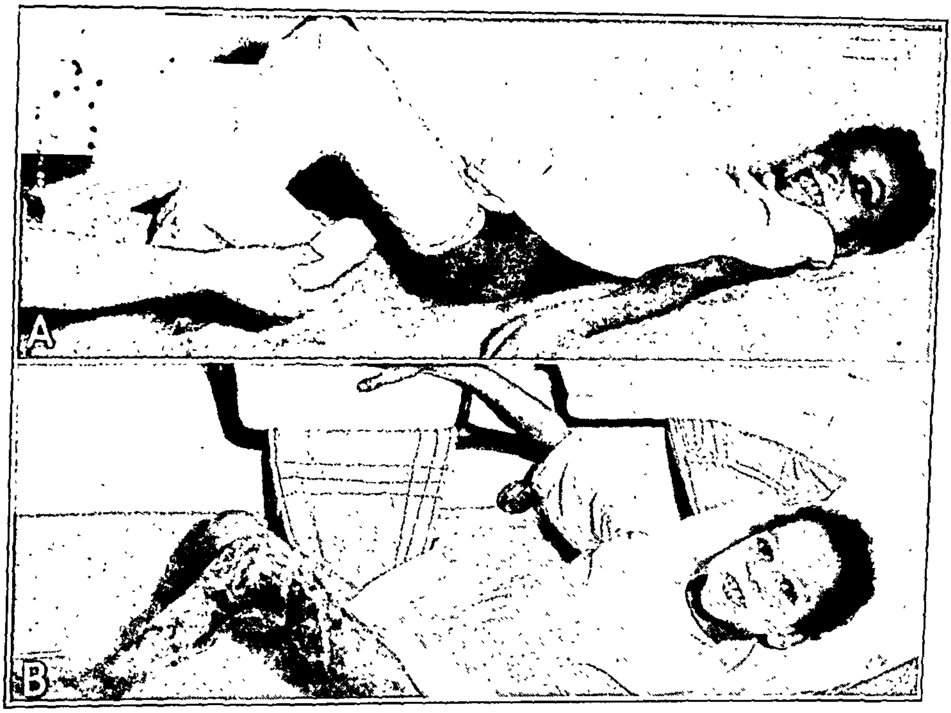

Fig. 3.—*A*, photograph of the method of applying a wet roller gauze roll to a wound when the time has arrived for separation of the dead tissues from the live soft tissues. Sufficient cotton pads are placed between the gauze to hold the moisture well. Externally a layer of rubber surrounds the gauze to prevent too rapid evaporation. Periodically the gauze is remoistened. The roll is changed morning and evening. *B*, if much pain is complained of when the roll is removed, if the condition of the patient permits he may be placed in a tub immersion for a few minutes and the gauze removed under water either by the patient himself or by the intern. The simplest solution to use is hypertonic saline solution. Any antiseptic solution, if nontoxic, will act the same.

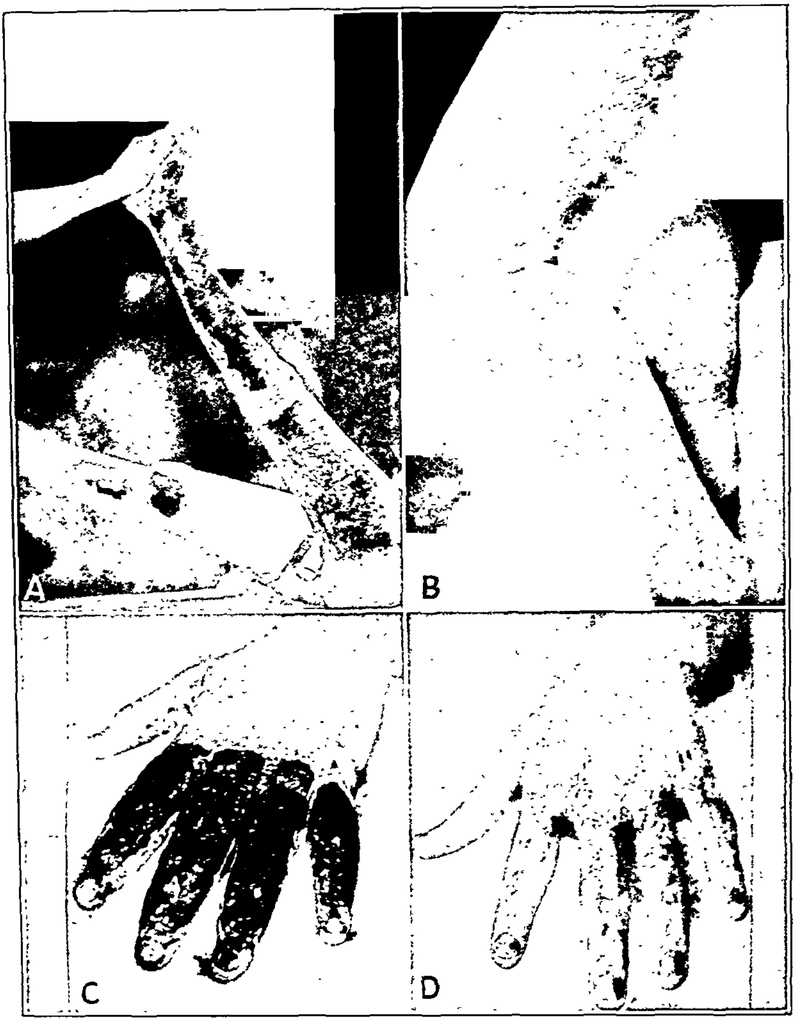

Fig. 4.—*A*, photograph of a large granulating wound of the leg of a patient ten days after beginning treatment by wet dressings and occasional tub immersion. She was burned thirty days before and was cared for at home by another physician, who used an ointment dressing which so far as the final result is concerned made little or no difference. An ointment dressing is, however, very "trying" on the patient and also on the one who has to do the dressing in the early days of the burn. A fixation method is a far more comfortable way of handling the situation. Whether or not it tends to prevent toxic absorption is quite another question. With the patient under gas anesthesia a large thin graft was applied from the opposite leg. Ninety per cent of the graft took. Thin grafts were taken from the inside of the left thigh, the outside of the right thigh and from the back. When taken along with the granulating area, owing to the burn such rather high percentage of body area was superficially denuded that about twelve hours after grafting skin from the inside of the right thigh, abdomen and back the patient showed signs of a mild "shock," which was interpreted as due to too wide an area of denudation (granulating area plus weeping area from which skin had been removed). A blood transfusion corrected this. *B*, photograph of the legs one year later. Extension and flexion were normal. *C*, photograph of a granulating wound three weeks after infliction of a burn from a clothes mangle. The tendons were destroyed. A wet dressing was used for one week before the photograph was made. Thin thick skin was grafted. *D*, photograph of the hand six months later. The patient obtained perfect flexion after the application of a thin graft to the granulating surface. Such a pleasant result does not often occur if the burn is of somewhat greater depth because of fibrosis of the tissues about the phalangeal joints.

the general condition of the patient, the factor of a relative secondary anemia was found to be important both as to the rapidity of epidermization and as an influence in obtaining a proper granulation bed on which a graft would "take." When the granulations were exuberant, a rather firm tight bandage aided in getting a firmer base. When evidence of anemia was present, a blood transfusion was given.

Grafting of Thin Skin on a Granulating Surface.[10]—The appearance of the granulating surface was used as the index to the time of grafting. The proper appearance was judged to be present when the surface was free from evidence of grayish slough or any gross pus and the granulation base was firm but not too exuberant or watery and was cherry red. Bacterial counts on smear were not considered of particular value. Anemic persons did not present granulation surfaces of the proper texture or color. Whenever grafting was attempted without the criteria being fulfilled, at least a part and usually most of the graft failed to "take." On the other hand, when it was present, practically in 100 per cent of the cases 90 per cent or more of the graft "took."

After laying the graft on the granulating surface, the same type of thick roller gauze dressing was applied as previous to grafting. This dressing was not changed for four or five days, and during this time it was kept saturated with saline solution or a saturated solution of boric acid. When the graft was located so that articular or muscular movement would probably cause it to slip, either stitches or a splint of some type or both were used so that fixation was definite.

A factor of particular interest to the surgeon is the reason for failure of a graft to "take." Of the 93 grafts applied to cover a granulating surface, in 42 there occurred a "take" of 90 per cent, which may be considered as practically perfect; in 13 there occurred a "take" of over 80 per cent, which may be considered as "good," and in 30 there occurred a "take" of over 70 per cent, which was usually sufficient so that further grafting to the granulating surface was not necessary. In 8 the loss ranged from 30 per cent to loss of the entire graft. The usual cause of loss was infection developing beneath a part or all of the graft. This usually was due to desultory preparation of the granulating surface, along with an error in judgment as to the time when the surface was in condition to receive a graft. In a few instances, improper fixation was the basic fault.

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[10] Possibly rather arbitrarily, a thin graft, to my mind, has been defined as any graft that leaves a part of the epithelial "pegs" in the area from which it was removed so that new skin regenerates from the bottom and the wound does not heal by growing in from the sides. Included in this definition would fall the "Thiersch" graft (Thiersch: Arch. f. klin. Chir. **17**:318, 1874) and the so-called "split" graft (Blair, V. P., and Brown, J. B.: The Use and Uses of Large Split Grafts of Intermediate Thickness, Surg., Gynec. & Obst. **49**:82-97, 1929) which is alleged to be a thicker graft than the Thiersch graft. At least the split graft places emphasis on the advantage of cutting a thick graft rather than a thin one.

In patients on whom the skin was grafted when the hemoglobin content was below 65 per cent it was estimated that the chance of a successful "take" with a thin graft on granulating surface was decreased from one-third to one-half because of a greater tendency for the graft to be destroyed by infection.

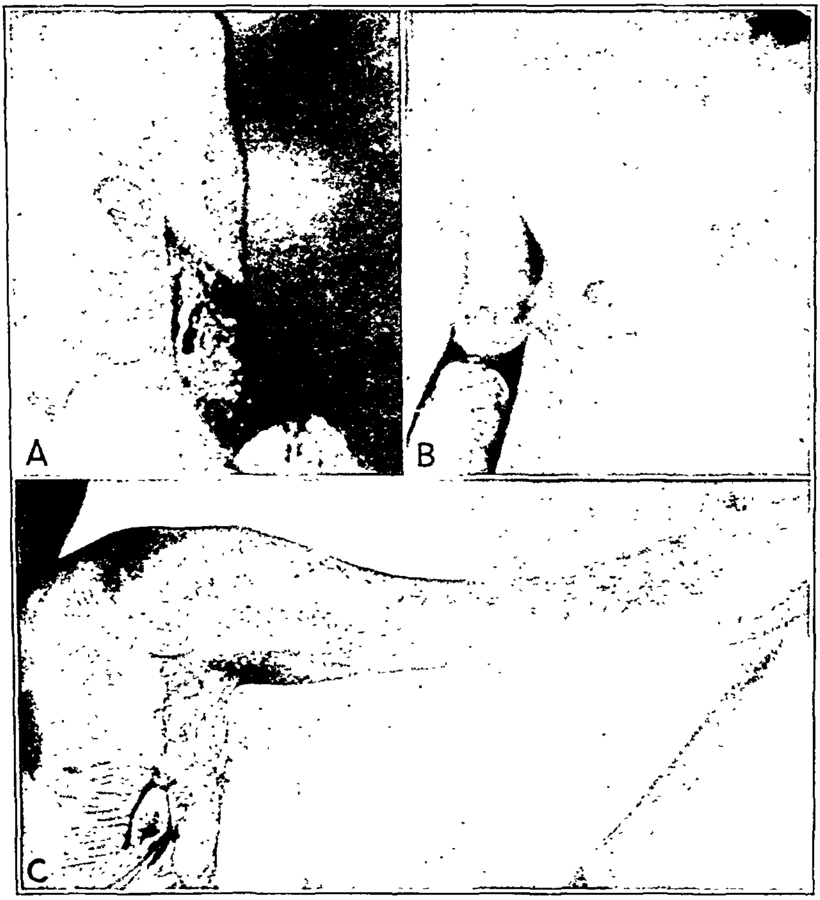

Fig. 5.—*A*, photograph of a granulating wound and cicatrix caused by an electrical burn inflicted eighteen months previously. The attachment of the triceps muscle to the olecranon had been destroyed. The patient could flex his arm by use of his biceps, and gravity caused extension. *B*, photograph of the front view of the healed cicatricial contracture of the axilla. *C*, photograph a few weeks after the application of a "split" graft to the axilla and to the granulating wound about the elbow. A little over 45 degrees of flexion was present.

When the granulating base was relatively new, a large thin graft showed a greater tendency to "take" well if the granulation tissue was not interfered with, but when sufficient fibrosis had occurred to give a firm scar base the chances of a complete "take" with a thin graft after the granulation and a part of the yellow scar base were sliced off were not decreased, and often some of the contracture was relieved, and better functional and cosmetic results were thereby obtained.

In several instances in which the patient was seen for the first time several months after the original injury and healed contractures had formed but part of the surface remained unhealed (fig. 5), it was often possible not only to cover the granulating area with a thin graft but to cross cut the contracture and largely correct the contractural deformity. In cases in which the contracture was graver, deformity was not always prevented, and the cosmetic result on such areas as the neck and face was often definitely unsatisfactory. Moreover, on such regions as the palm of the hand, the front of the leg and the bottom of the foot the amount of protection which a thin graft offered to the underlying tissues was not sufficient.

THE CORRECTION OF CICATRICAL AND COSMETIC DEFECTS AFTER COMPLETE HEALING

For the coverage of a fresh raw surface, I have used 165 thin grafts on 98 persons at 118 separate operations and 256 full thickness grafts[11] on 127 persons at 163 separate operations. Of the former grafts, 87, covering an average area of 29.5 sq. cm., were applied on 45 persons at 58 separate operations, and of the latter, 155, covering an average of 26.4 sq. cm., were applied on 67 persons at 91 separate operations to correct a healed cicatrix following a burn.

Chance of Failure of Graft to "Take."—Fortunately one seldom has to contend with the chance of not getting a good "take" when using a thick skin graft for the correction of a healed defect. When a full thickness graft is used to correct a healed defect, unfortunately one has to consider the possibility of a partial or even a complete failure to obtain a good "take." Of the 155 full thickness skin grafts used to correct the damage resulting from a burn, 130 showed (from 95 to 100 per cent) good "takes," which meant that a surgically clean surface was obtained, that the hemostasis was adequate, that the proper tension of transplanted skin was obtained, that the proper pressure was applied to gain coaptation between the graft and the bed and that adequate fixation or splinting was provided. In 3 instances the whole graft was lost. In 25 instances the loss was partial and ranged from 10 to 90 per cent. The causes of the loss were judged to be infection of all or of some part of the grafted area in 12 cases, lack of adequate pressure in 12, too much pressure in 1, blood clot in 2 and improper splinting which allowed muscular movement beneath the graft in 1.

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[11] A full thickness skin graft (Wolfe, J. R.: New Method of Performing Plastic Operations, Brit. M. J. **1**:360, 1875) is a free transplant which usually leaves no part of the epithelial "pegs" in the area from which it is removed. Section is made across the lower third of the corium. Unless the resulting wound is drawn together by sutures, the defect closes by a combination of fibrotic contracture and scarred epithelization.

Average Final Contracture of the Grafted Area.—Provided a good "take" occurred, the most important influence on functional result was the final amount of contracture of the grafted area. The subsequent average contracture of the full thickness skin graft when used in the correction of the damage resulting from a burn averaged 17 per cent and of the thin graft, 38 per cent.

Dressing for Grafts on Fresh Raw Surfaces.—As a rule, a graft applied to a clean raw surface was fixed by stitches, whether or not a thin or thick graft was used, a dressing of gauze treated with 5 per cent bismuth tribromphenate in petrolatum was laid on the graft and then a moderately thin layer of gauze was applied. Finally, a damp marine sponge was compressed by a bandage or stitches or both over the graft (fig. 6 *A* and *B*).

When movement seemed an eminent factor, some type of fixation by splinting was added. Externally, when the anatomy of the location was such that an outlay wax stent (fig. 6 *C, D* and *E*) gave better chances of the proper amount of pressure and tension on the graft, the tissue to be grafted was stitched about a wax form. Internally, within the mouth, as a rule, a wax stent was used.

The Selection of the Type of Graft.—My judgment as to the better type of graft to apply to a given region [12] under a certain group of circumstances has undergone considerable revision from time to time. Usually the ideal objective was balanced against the probability or the possibility of attainment in a reasonable manner.

When one wishes to correct a contracture about such a region as the axilla, the popliteal space or the elbow, full movement of the extremity is the first consideration. In the axilla it was found that a good "take" with a full thickness skin graft is somewhat difficult to obtain because of the likelihood of not getting uniform pressure. One does not encounter this difficulty about the elbow or the popliteal space. A proper amount of a thin graft will usually correct an axillary contracture (fig. 7 *A* and *B*). As this graft is the most certain to grow and the postoperative period of dressing is short, after making use of

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[12] Padgett, Earl C.: Full Thickness Skin Grafts in the Correction of Soft Tissue Deformities, J. A. M. A. **98**:18-23 (Jan. 2) 1932; Early and Late Treatment of Burns, J. Kansas M. Soc. **34**:184-188, 1933.

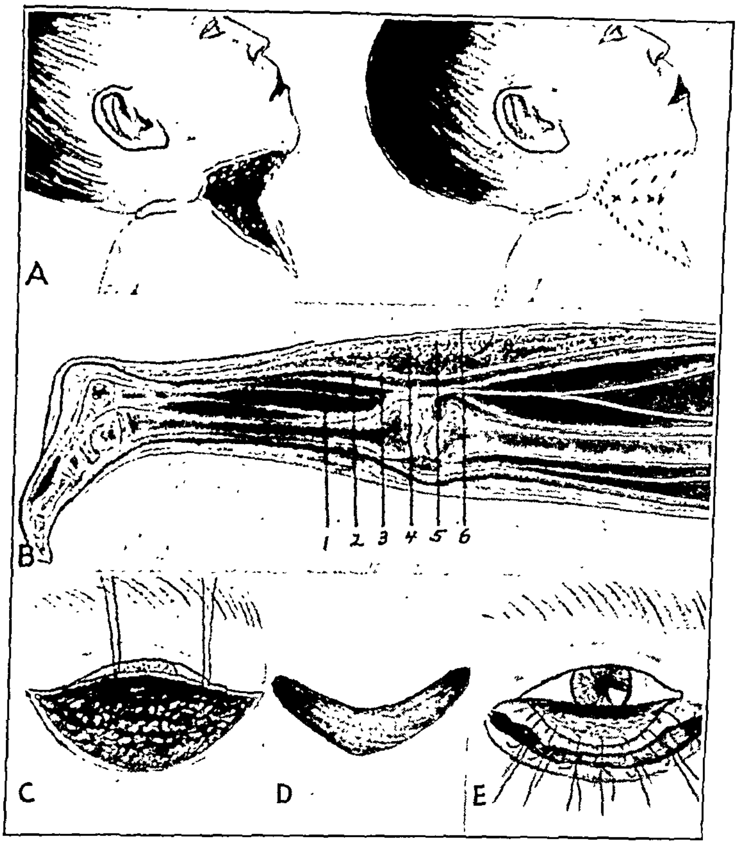

Fig. 6.—*A,* diagram of the method of cross-cutting a contracture and getting overcorrection. In this diagram a full thickness graft is shown stitched in place. In the gutter a few stitches were placed to aid in fixation. A few stab holes were made to prevent accumulation of fluid beneath the graft. When a thin graft was used the stitching was similar but looser, and the graft was made to overlap the edge of the skin. When more than one graft was used to cover the raw area, the grafts were overlapped and stitched through and through to the base beneath. *B,* diagram to illustrate the layers of the dressing: *1,* the graft; *2,* layer of bandage gauze impregnated with 5 per cent bismuth tribromphenate in petrolatum; *3,* thin layer of wet gauze; *4,* thick overlapping layer of marine sponge; *5,* moist cotton pad and firm bandage; *6,* possibly some type of splint to prevent movement. In this case an external cast was used. Often no splint is necessary. Whether a splint is needed for fixation depends on the location. *C,* diagram of an ectropion of the lower eyelid caused by a cicatrix which has been corrected by a lengthwise incision just beneath the eyelashes and cross-cutting of the cicatricial bands. *D,* diagram of a stent made of dental modeling composition before insertion over the muscle of the lower eyelid. *E,* diagram showing a method of wrapping a thick thin graft or a thin full thickness graft about the wax stent; by means of interrupted silk stitches pulled snugly over the stent the graft has been placed on tension and pressure given so that firm contact with the raw base is obtained. From 30 to 50 per cent overcorrection is made to allow for subsequent contracture.

any material available for a switch pedicled flap, a thin graft was usually used for the remainder of the raw surface in the axilla. The same was applied to perineal contractures. About the elbow and about the popliteal space, groin or back of the hand both types of grafts have been used, but because of the lesser tendency to contracture the full thickness graft was more often given the preference (fig. 8 *A* and *B*).

In cicatricial contracture of the palm of the hand (fig. 8 *C, D* and *E*) and the flexor surfaces of the fingers, the full thickness skin graft offered on the average a good functional result. Although a good "take" was more certain and the subsequent period of dressing was shorter, the thin grafts on the ventral surface of the fingers (fig. 9) between the fingers and over the dorsum of the hand usually did not give as satisfactory a result as did the thicker graft. The final contracture was greater, the appearance was not so near that of normal skin and in the case of ventral surface of the fingers the protection

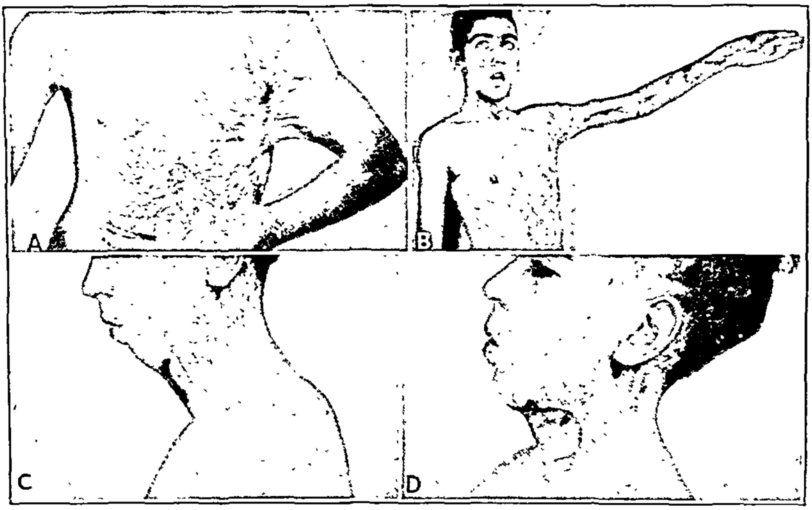

Fig. 7.—*A*, photograph of a healed cicatricial contracture of the left axilla, neck and thumb. *B*, a so-called "split" graft (a thick thin graft) was used for correction of the axillary contracture after cross-cutting the contracture. The photograph was made six weeks after the patient left the hospital. He was seen six months later, and the correction was complete. A full thickness graft was applied over the left thumb contracture. *C*, photograph of a neck contracture. The contracture was cross-cut, and a full thickness graft from the thigh was applied. As the patient was a boy and a collar would be worn it was considered that the essential factor was functional correction. *D*, lateral view of the neck six weeks later.

was not always adequate. The full thickness skin graft in the palm of the hand gave a good result functionally and cosmetically. The ultimate contracture was not so great that it could not be compensated for at the time of the operation, and the protection was adequate. After a graft was applied, some type of splint to hold the fingers of the hand in a position of overcorrection for several weeks aided the result very materially.

On the anterior portion of the neck a thin skin graft, although almost certain to "take," usually contracted from 50 to 70 per cent, too greatly to correct the contracture, and the appearance usually was not satisfactory. In over 80 per cent of the attempts a good "take" after the application of a full thickness skin graft to the upper and anterior portion of the neck was obtained. When this occurred the contracture was corrected in from one to two operations, and the cosmetic result was good. The swallowing movement usually caused some loss of a

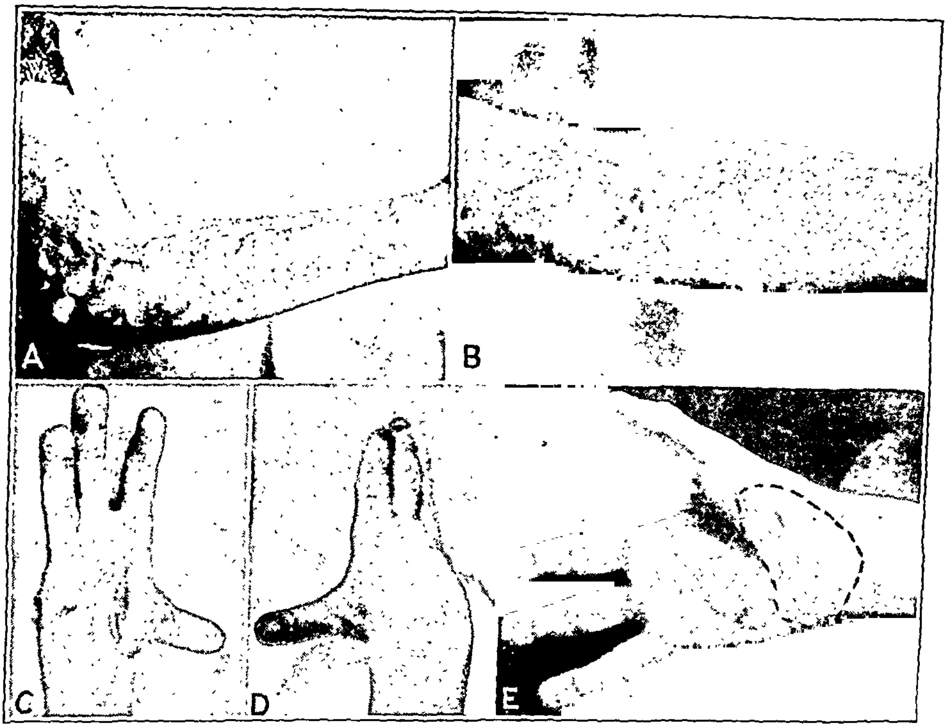

Fig. 8.—*A*, photograph of a contracture of the region of the elbow. *B*, photograph made two months after release of the contracture and application of a full thickness skin graft. *C*, photograph of a contracture of the palm of the hand, palmar view. *D*, dorsal view of the hand. The little finger was removed at some previous operation. The contracture was cross-cut, and a full thickness skin graft was applied. *E*, photograph of the preceding hand eight months later. The graft lies within the dotted line.

graft over the thyroid cartilage no matter what type of dressing was used with the idea of preventing it. In later cases an attempt was always made not to leave a raw area over this region.

After both thin and full thickness grafts had been tried out over the thyroid cartilage, the adjacent sides of the cheek and the mandible, it was found that the latter usually was given the preference, because the full thickness graft more nearly approximated the normal skin in appearance (figs. 10, 11 *A* and *B* and 12). On the sides of the face the full thickness graft has been given a decided preference. In these regions the final result after a satisfactory "take" of a full thickness graft justified the risk of not getting a good "take." Some of the most brilliant results were obtained with large full thickness grafts to the face. Although in several instances the appearance of the graft was somewhat whiter than normal skin, a thick thin graft gave a satisfactory result when applied over the orbicularis oris muscle for an ectropion of the upper or the lower lip.

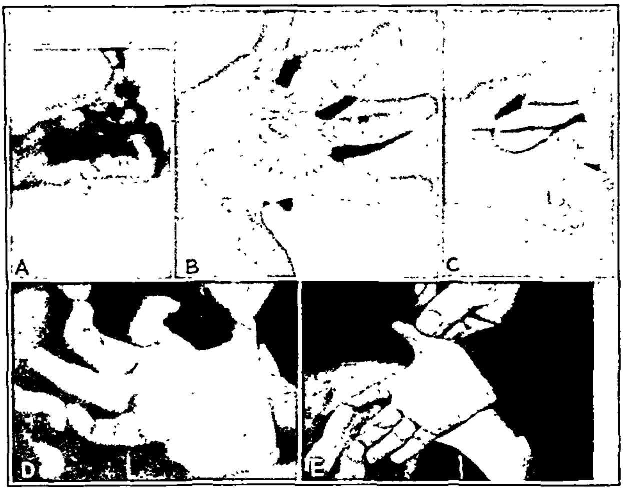

Fig. 9.—*A,* photograph of a ventral cicatricial contracture of the fingers of the right hand. The scar was cross-cut, and a full thickness skin graft was applied. *B,* a photograph three months later showing extension. *C,* made at the same time, shows flexion. *D,* contracture of the thumb and first finger. The contracture was cross-cut, and a full thickness skin graft was applied. *E,* a photograph made three months later.

When a full thickness skin graft was used on the neck and chin, about the mouth and over the cheek, in at least half of the cases a secondary operation was found to be necessary after a period of several months, for the purpose of excising the rather heavy scar which often forms at the juncture of a full thickness skin graft with the surrounding normal skin. Moreover, even in advent of obtaining a good "take" of a full thickness skin graft on the face, the possibility had to be considered of having the graft appear too shiny or in brunettes of presenting a discoloration from pigmentation. Although there was a tendency for the full thickness graft to have a slightly shiny appearance, most of the grafts that "took" well without much superficial exfoliation eventually showed grossly almost the normal texture of the skin of the region from which the graft was removed. Those grafts in which some superficial exfoliation occurred had more of a tendency to show pigmentary changes. In pronounced brunettes, pigmentation sometimes occurred in a perfect "take."

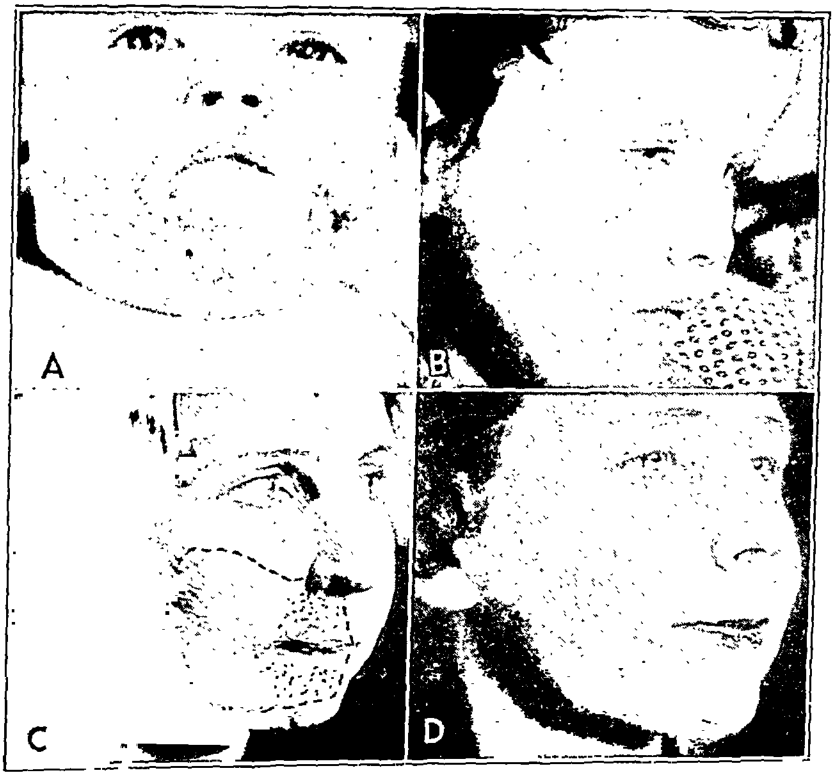

Fig. 10.—*A,* photograph of a cicatricial keloidal contracture of the side of the face. The scar was removed, and a full thickness skin graft was applied. *B,* a photograph made two years later. *C,* photograph of a scar of two thirds of the side of the face and extropion of the upper and the lower lid. A full thickness skin graft was applied to the side of the face. The dotted outline shows the extent of the scar. Over the dotted area on the region of the upper and the lower lip a heavy split graft was used. *D,* photograph of the final result two years later after excision of surrounding scar.

On the sides of the neck, over the sternocleidomastoid muscle and the posterior portion of the neck a thin graft was found to give an acceptable result functionally and cosmetically. Here the contracture was usually less than one-third. Because of the ease of application and the certainty of a "take" in this region, the thin graft was given preference.

When a muscle was near the surface, as about the eyelids (fig. 11, *C* and *D*), about the lips or over the sternocleidomastoid muscles on the side of the neck, the results obtained after the application of a thin graft were as good or in rare instances even better than that after obtaining a good "take" with a full thickness graft. When such is the case, the greater likelihood of a perfect "take" after the application of a thin graft, the shorter period for postoperative dressing and the probability of only a slight cicatrix at the junction of the graft with the normal skin speak strongly in favor of the thinner graft. For this reason about the eyelids most often a relatively thick thin graft draped about a wax form was used, but more rarely a thin full thickness graft

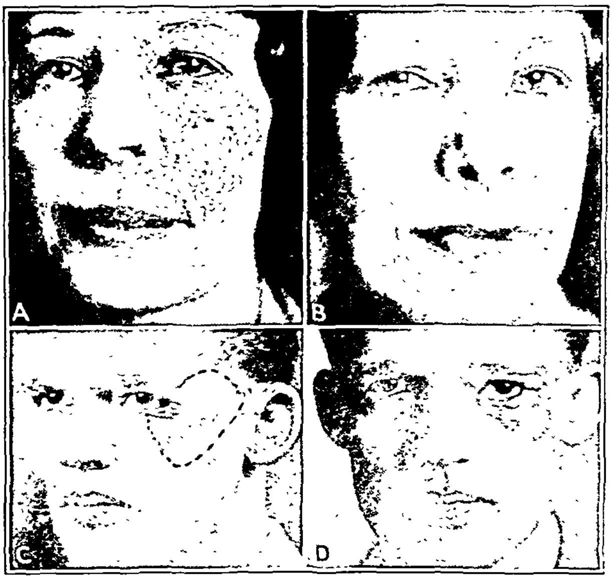

Fig. 11.—*A*, a photograph of a large hemangioma of the face which had been burned by the x-rays and radium. The area showed telangiectasis and mottled and scaly patches. Complete removal was carried out, and a large full thickness skin graft was applied. *B*, a photograph of the result one year later. *C*, a photograph of ectropion of the lower eyelid with destruction of the outer canthal region. The scarred side of the face is shown by the dotted outline. After excision of the whole scar, a large heavy split graft was applied to the temporal region and the side of the face and a thick thin stent graft was used over the eyelids. *D*, a photograph of the result two years later.

from back of the ear was used. Probably the latter method most nearly approached the ideal about the eyelids.

Acceptable eyebrows were made with a full thickness graft from the scalp. The hair was found to be somewhat sparse and less plentiful than in a normal scalp, but with care in clipping the new eyebrow was fairly successful.

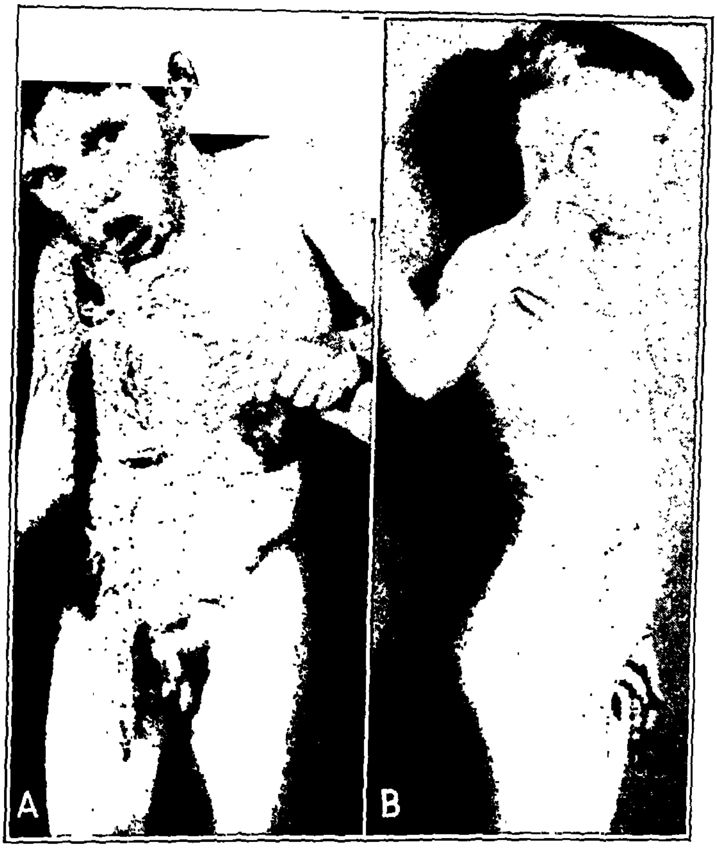

Fig. 12.—*A,* a photograph of a severe burn with a partially healed cicatrix. Multiple skin grafting operations were carried out after the contracture was crosscut, which was to be corrected at the given operation. Note the contracture of the neck, about the lower lip and axilla and over the groin. The right thigh was pulled into a position of nearly 45 degrees flexion. The boy lay in bed in an almost vertical ball. A "split" graft was used for the axilla and the right groin. Full thickness grafts were used for the neck and chin, beneath the lower lip and behind the right ear to release it from his head. *B,* a photograph of the general result eighteen months later.

THE PRACTICABILITY OF HOMOGRAFTING

In 1932 I published my results with 44 experimental isoskin grafts, or homografts.[13] Since that time the experiment has been repeated in

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[13] Padgett, Earl C.: Is Skin Grafting with Isografts or Homografts Practicable, West. J. Surg. **41**:205-212, 1932; Is Skin Grafting with Isografts or Homografts Practicable? Surg., Gynec. & Obst. **25**:786-787, 1932.

6 cases. My data show that the result to be expected after isodermic transplantation by ordinary methods, at least, may be summarized as follows: An immediate "take" occurs in the majority of cases. In nonrelated persons, between the second and the third week the grafts begin to disappear, and by the end of the fourth week they have completely disappeared. In persons related by blood (syngenesiotransplantation), such as father and son or even uncle and nephew, the grafts "take" and remain viable about three weeks, but by the end of the fifth week they are destroyed. In identical twin transplantations (the closest possible syngenesiotransplantation or "near relation transplantation") the grafts may remain. Syngenesiotransplantation of skin is theoretically improbable except in identical twins, in whom it is theoretically probable and clinically has occurred. The failure of experimental isodermal grafts on man and on animals to remain viable or to show a relationship to the blood group in the length of time viability is present and theoretical reasoning argue against the blood group of the patient as playing a rôle of any essential significance in homotransplantation of the skin. The bulk of experimental and clinical experience is in agreement that isotransplantation or homotransplantation of skin is not practicable except possibly in identical twins. Thus, some antagonism not as yet understood apparently exists between the cells of the host and the donor, even in close relatives, and as the distance of the relationship within the species is increased progressively the antagonism is more marked. Moreover, without species the antagonism is even more marked than within species. The great importance of the relative nearness of the relationship of the genes of the host and the donor of the transplant is apparently the crux of the matter.

SUMMARY

Of a series of 514 skin grafts transplanted at 361 separate operations on 257 different persons, 299 were transplanted at 193 separate operations on 144 persons to alleviate a burn.

To exemplify the problems encountered in the care of a severe burn in the early, the intermediate and the late stage, a series of 144 burned persons was found to present the necessary situations.

In the care of the severely burned greater emphasis should be focused early on alleviation of the profound systemic disturbance than is placed on the care of the local lesion.

The recognition of the depth and the area of complete epithelial destruction is an essential point to be grasped if one is to understand the principles of reepidermization and the basic cause of contractural deformity.

Early resurfacing after a large complete loss of skin should always be the goal of the efficient surgeon because of the decrease in the period of convalescence with its economic potentialities and the prevention of contractures with the functional incapacitation which accompanies them.

Provided the general condition of the patient is good, one's success in growing thin skin grafts on a granulating surface is directly proportional to the general cleanliness of the surface.

In an anemic person the chance of a good "take" on a surface of granulation tissue is decreased.

In the successful grafting of skin dependence on simple fundamental principles and methods, in contradistinction to a special type of graft with or without a "far-fetched" method of placement or puncturing or dressing, is important.

In the correction of cicatricial defects after complete healing has occurred, the decision whether to use a thin graft or a full thickness graft depends on a careful balancing of the characteristics of the two grafts, the main object to be attained in a given region and the relative risk of failure to get a good "take." Sometimes the disability entailed in the removal of the graft and the length of the period of postoperative dressing also become factors to be considered.

After observing a series of 50 experimental homotransplants in man, the conclusion was reached that isodermal grafting is not a practicable procedure unless an identical twin is available.

ABSTRACT OF DISCUSSION

DR. G. B. NEW, Rochester, Minn.: As Dr. Padgett has brought out, the treatment of extensive burns should always be considered an emergency of the greatest importance. To obtain the best results, treatment should be directed as soon as possible by the combined efforts of a team consisting of an internist, a biochemist and a surgeon.

In a recent symposium, Osterberg showed that the clinical picture observed in cases of extensive burns is due to excessive concentration of the blood with its resultant phenomenon and not to specific toxins produced as a result of the burning of the tissues. Bannick and Keith emphasized the necessity in cases of extensive burns of early relief from pain by the administration of morphine in order to prevent shock and of relief from marked dehydration. They urged that fluids be replaced early by sodium chloride and dextrose solutions.

The surgeon must cover the raw surfaces with a tannic acid spray as soon as possible. Seeger, however, has shown that there is no reduction in the ultimate mortality which can be attributed to the use of tannic acid, other factors in the treatment being comparable. The mortality has been reduced in the first five days, many of the patients dying, however, in the later stages. Of 369 cases of burns in the Milwaukee Children's Hospital, 39, or approximately 11 per cent, were fatal; of 197 cases in which tannic acid was used, 23, or 12 per cent, were fatal; of 172 cases in which other methods of treatment were used, 16, or 9 per cent, were fatal.

Brown and Blair's excellent work on the use of baths of hypotonic saline solution and early covering the raw areas with shaved skin grafts has been one of the most striking advances that I have seen in the treatment of burns. The type of skin grafting employed must depend on the usual factors in determining the use of skin grafts in general. When the granulated area is ready for grafting, a shaved graft will cover the area with a high percentage of "takes," but when such a graft is used about the face and neck, there is usually a great deal of contraction, and the color is frequently not satisfactory. A secondary free full thickness skin graft or a skin flap becomes necessary. When a full thickness skin graft is used about the cheeks, submental or submaxillary region, wiring the upper and the lower teeth together as one would in a fracture of the lower jaw, the patient being fed with a Rehfuss tube, prevents any movement, thus adding considerably to the percentage of "takes." A free full thickness skin graft is best used over the muscles of expression, as it is almost impossible to get a flap thin enough so that the muscles show through. The color, of course, in the flap is much more satisfactory than can be obtained by a shaved or free skin graft. A large tube flap taken from the chest with one pedicle in the infraclavicular region and the other well down on the chest gives excellent results. The area in the infraclavicular region simulates closely the skin of the face and neck in color and texture and makes ideal material for this purpose. The lower end of the tube flap on the chest is carried to the neck or region of the mastoid, and then the skin in the infraclavicular region is carried to the neck or face where it is to be utilized. If the full thickness of the nose or cheek has been destroyed, it is necessary to line the area in the infraclavicular region with a full thickness skin graft in order to prevent the transferred skin from pillowing. In the cases with scarred band contractures, the use of the Z or VY incision operation will release them and correct much of the deformity. Dr. Padgett's results in this work have been extremely good, and he should be highly complimented.

Dr. James Barrett Brown, St. Louis: Although there are many reports on the treatment of burns, the small number of authors who publish final results as to healing and function in large series of patients who have lost the full thickness of the skin over a wide area is small. The late care and repair in such cases may require more time-consuming and exacting work than the primary treatment.

When deep burns heal there are contractions of the surrounding tissue and final closure of the defect by "scar" epithelium growing in from the sides. This scar epithelium is thin, contains no hair or sweat glands and lies flat on fibrous scar tissue that has no papillary layer or other semblance of normal derma. This condition does not change throughout years except that there may be some softening. There may be a general shortness of the skin necessary for function; over weight-bearing areas there may be chronic ulceration, and in any area this thin scar epithelium is subject to rapid and wide loss from infection or trauma. Microscopic studies of a large number of scars have shown this plainly, and on several occasions I have taken specimens for biopsy from areas that have been traumatized and have found the entire "scar" epithelium grossly dissected loose from the underlying fibrous tissue by hemorrhage.

The substance of the care of areas in which there is an extensive loss of the surface is that they should be repaired as soon as possible with skin grafts. The main difference in my method of repair in such cases from that discussed by Dr. Padgett is that I limit the number of full thickness skin grafts and substitute a graft that includes from one third to three fourths of the thickness of the derma. This graft might be called a thick Ollier-Thiersch graft, but the term thick split graft may be used to identify it from the thin, almost useless Ollier-Thiersch graft and from the full thickness graft.

The thick split graft may be cut rapidly and easily in large pieces and will "take" almost as successfully as the thin Ollier-Thiersch graft. It does not give as good immediate result as the full thickness graft, but it may be risked on open wounds, and perhaps its greatest advantage is that healing of the site from which the graft is taken occurs rapidly, in contradistinction to the great trouble experienced in getting the sites from which large full thickness grafts are taken to heal. I have grafted 173 square inches of this type of graft at one time. Healing progresses toward the surface from the deep glands in the derma, and microscopic studies have shown complete surface coverage as early as the sixth day. This process is a "dedifferentiation" of the epithelial cells and progresses in the opposite direction of the growth of a cancer. A semblance of the picture of actual cancer may occasionally be seen in examination of this surface healing process in different stages.

One of the main uses of this type of graft is in effecting major repairs with a minimum of time and operations. The repair of badly contracted axillary and popliteal regions seldom requires a full thickness graft or pedicle flap, and, at least for the primary release of contractures about the neck, the thick split graft may be used to get the head up and the mouth closed and to allow the patient to resume a normal social and economic status. Then, if there is too much roughness or recurrent deformity, any other method of repair may be used.

Dr. Earl C. Padgett, Kansas City, Mo.: Possibly I have favored the full thickness skin graft a trifle more than is necessary. A certain amount of idealism has entered into the matter. When a good "take" of the full thickness graft is obtained, it undoubtedly in certain instances has qualities superior to those of any other graft. This is true especially for the face and neck. It would seem that with the use of a procedure with which one can succeed completely in 80 per cent of the attempts and can obtain partial success in another 15 per cent of trials, if a little more could be learned of the reasons for failure and certain adverse factors eliminated, one should succeed in nearly 100 per cent of the trials. I have succeeded in obtaining a good "take" in 5 cases of hemangioma of about one half of the face. Such an operation is heroic, but in adults I believe that it gives a result when successful which cannot be approached by other methods. An occasional failure in growing a full thickness skin graft, however, must be expected. I have had a failure after excising a large cicatrix of the face following a burn. The principles that make for success are the same, however, after excision of either lesion—a cicatrix or a hemangioma.

SURGICAL DISEASE OF THE GALLBLADDER

CLINICAL AND PATHOLOGIC REVIEW OF THE DISEASE IN 133 PATIENTS OPERATED ON AT THE MOUNT SINAI HOSPITAL, WITH FOLLOW-UP STUDIES

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The incidence of disease of the gallbladder in the adult population, the term being limited to include calculous and noncalculous cholecystitis, is very high. Stewart, of the University of Leeds, is quoted by Blackford, King and Sherwood (cited by Palmer[1]) as reporting evidence of disease of the gallbladder in 16.4 per cent of 6,000 routine autopsies. Blackford and his associates concluded that more than half of the adults past 30 years of age have abnormal gallbladders and that approximately one fifth of these have gallstones. According to the statistical studies of Graham and his co-workers (cited by Hauser[2]), from 20 to 25 per cent of all adults have gallstones and probably an equal number have cholecystitis without stones. Thus, about 40 per cent of the adult population have disorders of the biliary system, which in probably the majority of instances are at times associated with more or less severe symptoms. McEvedy[3] found that calculi are absent in 20 per cent of persons with definite cholecystitis, whereas in a small percentage of patients with gallstones the gallbladder shows no definite change or evidence that the inflammation has followed the calculi. Moynihan (cited by Burton[4]) said that "all gall-stones except pure cholesterin calculi invariably cause symptoms."

From the Laboratories and Surgical Departments of the Mount Sinai Hospital.

[1] Palmer, W. L.: Gall Bladder Disease: Remarks on Symptoms, Diagnosis, and Treatment, Internat. Clin. **1**:111-123 (March) 1935.

[2] Hauser, H.: Practical Application of Cholecystography, Radiology **21**: 472-477 (Nov.) 1933.

[3] McEvedy, P. J.: Gall Stones and Cholecystitis, Clin. J. **64**:111-115 (March) 1935.

[4] Burton, J. A. G.: Cholelithiasis: A Summary, Glasgow M. J. **121**:14-23 (Jan.) 1934.

Although the literature is replete with clinical reports and follow-up studies of cases of disease of the gallbladder, there have been few studies dealing with the relationship between the pathologic changes found at operation, the results of the histologic study of operative specimens and the clinical course in any particular series of cases of this disease. In the present study it has been our purpose to correlate the histologic structure and the gross pathologic picture of the gallbladder found or removed at operation with the clinical symptomatology and the subsequent results of operative treatment in those cases in which follow-up studies were possible. With this in view, we have made a complete and careful study of 133 patients with disease of the gallbladder who were treated at the Mount Sinai Hospital from 1930 to 1935. Follow-up data were obtained in 61.6 per cent of the group. Patients with malignant growths of the biliary tract or persons who were not operated on were not included. The results thus obtained have been critically correlated with the histopathologic picture. Coincidentally, an attempt has been made to analyze the causes of morbidity and mortality with the purpose of recognizing pathologic conditions corresponding to the clinical course.

The controversy over the advantages of cholecystostomy as compared with cholecystectomy seems at present to have abated, but it is by no means conclusively settled. Surgeons now agree that an infected gallbladder is incapable of being restored to normal function (Graham [5]) and may also act as a focus of infection. Moreover, the degree of disability which a patient suffers as the result of a diseased gallbladder is dependent not only on the changed content of the gallbladder and the involvement of its wall but on the associated involvement, for which the diseased gallbladder may be in part responsible, of the pericholecystic structures, i. e., the liver, pancreas, duodenum and common bile duct.[6]

Hartmann, Alvarez, Deaver, Zinc and others (cited by Mackey [7]) concluded from their findings that the results of cholecystectomy in cases of cholecystitis without stones are better than the results in cases of frank cholelithiasis. They explained their findings by the assumption that cholecystitis without stones represents the earliest stage of disease of the gallbladder and expressed the belief that when the stage of cholelithiasis has been reached there have developed, in a large proportion of cases, lesions in other viscera, which persist after cholecystectomy and continue to cause symptoms. On the other hand, Flörcken, Gundermann, Seuleberger, Hitzrot and Cornell, Müller, Lahey and others (cited by Mackey[7]) found that the clinical results of cholecystectomy were better in cases of cholelithiasis. In many cases in which the stoneless gallbladder was removed at operation but symptoms have persisted, they argued that the gallbladders have not been the cause of the symptoms with which they have been libeled. On the basis of a statistical study, Peterson[8] stated that favorable results were obtained with cholecystectomy in cases of cholecystitis associated with stones, i. e., cure in 83 per cent, while in cases of cholecystitis without stones the operation resulted in cure in only 52 per cent. Cholecystostomy alone in cases of each type resulted in a cure in 52 per cent. Mackey,[7] after reviewing 6,000 cases reported in the literature, summed up the evidence obtained as follows: "The experience of a large number of surgeons in the past has shown that cure or improvement after cholecystectomy may be expected in nearly 90 per cent of cases of cholelithiasis and in nearly 80 per cent of cases of cholecystitis without stones." Others like Judd and Priestley and Hueck (cited by Mackey[7]) could find no appreciable differences in the results following operation in these two types of cases.

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[5] Graham, R. R.: Surgical Therapy in Gall Bladder Disease, Canad. M. A. J. **30**:119-123 (Feb.) 1934.

[6] Deaver, J. B.: Causes of Morbidity and Mortality of Operation for Gall Stone Disease, Surg., Gynec. & Obst. **49**:308-315 (Sept.) 1929. Graham.[5]

[7] Mackey, W. A.: Cholecystitis Without Stone: Investigation of Two Hundred and Sixty-Four Operated Cases from the Clinical, Radiological, and Pathological Aspects, Brit. J. Surg. **22**:274-295 (Oct.) 1934.

In our group of patients there were 15 with cholecystitis without stone formation who came to operation. Of this number, follow-up information was obtained on 7. Mackey,[7] in a similar study, found that the results were usually more gratifying in cases in which the clinical symptoms were well marked than in those in which the symptoms were not marked. It appears also that the removal of those gallbladders which presented definite pathologic changes yielded better clinical results than excision of gallbladders in which the pathologic changes were minimal.

Since our group of patients with noncalculous cholecystitis is small and the results obtained by study were in agreement with those reported by Mackey,[7] we have made a composite table of the data in each group. which illustrates the findings discussed very clearly.

Of our series of 118 patients with cholecystitis with stone formation, 110 were treated by cholecystectomy; of these, 6 died after operation (table 2). The remaining 8 were treated by cholecystostomy, and of these, 3 died. The high mortality (37.5 per cent) after cholecystostomy may be explained by the fact that this type of operation is employed at the Mount Sinai Hospital only on patients whose general condition precludes the employment of any drastic form of surgical intervention.

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[8] Peterson, T.: Gall Bladder Disease: A Critical Clinical Study, Minnesota Med. **18**:123-127 (Feb.) 1935.

Lipshutz,[9] in a recent study, concluded that the operative mortality in cases of acute cholecystitis is less when operation is performed as soon as the patient has been adequately prepared with dextrose and fluids than when operation is deferred. Mentzer,[10] in a study of 43 cases of acute cholecystitis, found that what appears to be a mild or moderately severe cholecystic inflammation clinically may actually be a fulminant cholecystitis. Mentzer, Kirschner and Nordmann (cited by Bashein[11]) and many other surgeons advocate early operative intervention, usually cholecystectomy, in cases of acute cholecystitis. The findings in our present study are in accordance with this point of view. Twenty-two patients with acute cholecystitis associated with stones were treated by cholecystectomy, with 1 death, a mortality of 4.5 per cent. Seven patients with acute cholecystitis were treated by cholecystostomy, with 2 deaths, a mortality of 28.5 per cent.

TABLE 1.—*Correlation of Pathologic Changes, Clinical Symptoms and End-Results in 147 Cases of Cholecystitis Without Stones*

		Results in Cases With History of Biliary Colic (52)			Results in Cases Without History of Biliary Colic (95)		
	Pathologic Lesion Present	Well	Improved	Unimproved	Well	Improved	Unimproved
Mackey's cases	Minimal lesion	2	6	7	9	15	15
	Cholesterosis	8	0	5	6	2	11
	Chronic catarrhal cholecystitis	10	6	1	7	12	13
	Chronic fibrous cholecystitis	1	1	0	1	2	0
Authors' cases	Chronic fibrous cholecystitis	2	3	0	0	0	2
	Total of both groups	23	16	13	23	31	41

The average period of preparation for the patients with acute cholecystitis who were subjected to cholecystectomy ranged from two and four-tenths to three and six-tenths days (table 2). The average period of convalescence of these patients with acute gangrenous calculous cholecystitis and acute exacerbation of a chronic calculous cholecystitis was thirteen and a half days. Three patients with acute ulcerative calculous cholecystitis had an average convalescence of eighteen and three-tenths days. The average period of preoperative hospitalization for the 88 patients with subchronic and chronic cholecystitis was about nine days, as compared with the average of three days for those with acute cholecystitis. This is explained by the fact that many of the patients in the first two groups were usually admitted to the medical services for complete study before being subjected to operation.

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[9] Lipshutz, B.: Acute Cholecystitis, Ann. Surg. **101**:902-911 (March) 1935.

[10] Mentzer, S. H.: Acute Gall Bladder Manifesting Few Signs or Symptoms, Surg., Gynec. & Obst. **55**:709-716 (Dec.) 1932.

[11] Bashein, H.: Gall Bladder Surgery: Observations from Series of Cases as to Advantages of Early Operations, Am. J. Surg. **23**:506-513 (March) 1934.

We were able to obtain follow-up data on 17 of the 29 patients with acute cholecystitis who were operated on. All 17 were either completely cured or else greatly improved. This finding is in sharp contrast to the results obtained by cholecystectomy in cases of noncalculous cholecystitis, as shown in table 1; in a series of 147 patients, 56, or 38 per cent, failed to be relieved or were made worse by the operation.

Of the 88 patients with subchronic or chronic cholecystitis with stone who were treated by cholecystectomy, 6, or 6.8 per cent, died after operation. Of the remaining 82, we were able to obtain follow-up data on 50. In this group 28 regarded themselves as cured, and 21 stated that they were greatly improved, suffering only from occasional attacks of dyspepsia after dietary indiscretions. Only 1 patient in this group was found to be unimproved. Thus, of the group of 104 patients with calculous cholecystitis who survived cholecystectomy, we were able to obtain follow-up data on 63. Of these, 62, or approximately 98 per cent, were either cured or greatly improved, while only 1 patient showed no improvement.

Statistical and follow-up data in the recent literature on cases of disease of the gallbladder[12] are in overwhelming agreement as to the most important criteria for establishing a diagnosis of such a condition.

1. A typical history, which includes intermittent pain in the right upper abdominal quadrant, with or without jaundice, and a persistent gaseous indigestion characterized by a qualitative dyspepsia for fried and fatty foods, is an important indication. According to Stanton,[12a] if a surgeon is definitely certain of his ground relative to the clinical history of biliary colic, he can proceed to remove the gallbladder even if there is no obvious recognizable pathologic process present at the operative table.

Table 3 shows that colic, which was present in 112 of 118 cases of various types of cholecystitis, is the most constant clinical symptom and substantiates what Stanton has said about the significance of biliary colic. Additional justification for the removal of the gallbladder in these cases may be found in the fact that of the 63 patients on whom a follow-up study was made, 62 were either cured or greatly improved.

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[12] (*a*) Stanton, E. M.: Stoneless Gall Bladder: Study of Operative Cases, Am. J. Surg. **18**:246-250 (Nov.) 1932. (*b*) Hitzrot, L. H.: Correlation of Other Diagnostic Procedures with Cholecystography in Two Hundred and Fifty Cases of Suspected Gall Bladder Disease, Am. J. M. Sc. **186**:203-213 (Aug.) 1933. Mackey.[7]

TABLE 2.—*Correlation of Pathologic Changes and Clinical Course in 118 Cases of Calculous Cholecystitis*

Pathologic Lesion Present	No. Cases	Duration of Symptoms				Period of Preparation	Average Postoperative Period in Hospital	Results of Follow-Up Study				No. Without Follow-Up Study
		1 Yr.	1-5 Yr.	5-10 Yr.	Over 10 Yr.			Died	Well	Im-proved	Unim-proved	
Cholecystectomy (110 Cases, with Follow-Up in 62)												
Acute gangrenous cholecystitis...........	13	5	8	0	0	2.4 days after admission (12 cases), 41 days (1 case)	13.6 days	0	4	4	0	5
Acute ulcerative cholecystitis.............	3	3	0	0	0	3.6 days	18.3 days	0	0	2	0	1
Acute exacerbation; chronic cholecystitis	6	2	0	0	4	3.5 days	13.0 days	1	2	1	0	2
Subchronic cholecystitis..................	41	5	15	14	7	9.2 days	15.4 days	2	14	8	0	17
Chronic cholecystitis......................	47	8	21	7	11	8.7 days	14.2 days	3	13	13	1	17
Total....................................	110	23	44	21	22			6	33	28	1	42
Cholecystostomy (8 Cases)												
Acute ulcerative cholecystitis.............	1	0	1	0	0			1	0	0	0	0
Acute exacerbation; chronic cholecystitis	6	2	3	1	0	Immediate (3 cases), 10.5 days (4 cases)	26.4 days	1	4	0	0	1
Chronic cholecystitis......................	1	0	0	0	1			1	0	0	0	0

2. The cholecystogram is the most important single clinical test in establishing a positive diagnosis of disease of the gallbladder. Rose[13] summarized the work of 20 authors, reporting a total of 39,280 cases, in 5,983 of which operation was performed, and added 911 cases of his own, in 295 of which operation was performed. He concluded that the roentgenographic diagnosis of a pathologic process of the gallbladder is dependable to the extent of 98 per cent. Ferguson and Palmer,[14] in a review of 2,070 cases extending over a period of five years, arrived at approximately the same conclusions as Rose. However, the roentgenographic diagnosis of a normal gallbladder is correct, on the average, in only about 76 per cent of the cases. This finding may be explained, according to Burden,[15] by his observation that an incompetent sphincter of Oddi will not permit of proper filling of the gallbladder or of concentration of its contents. On the other hand, a spastic sphincter, which is frequently present in cases of cholecystitis, will allow and even promote proper filling and concentration in the gallbladder, thus giving rise to a normal cholecystogram even though the gallbladder is diseased.

TABLE 3.—*Correlation of Pathologic Changes with Clinical Symptoms and End-Results in 118 Cases of Calculous Cholecystitis*

Pathologic Lesion Present	No. of Cases	Jaundice	Qualitative Dyspepsia	Colic	Well	Improved	Unimproved
Acute gangrenous cholecystitis	13	4	3	13	4	4	0
[illegible]	4	1	0	4	0	2	0
[illegible]	12	4	5	12	2	1	0
[illegible]	41	10	19	39	14	8	0
[illegible]	48	12	17	44	13	13	1
Total	118	31	44	112	33	28	1

According to the statistics of Moore,[16] Hauser,[2] Clute and Swinton[17] and Hitzrot,[12b] the diagnosis based on the cholecystogram is correct in 90 per cent of the cases and is of equal value whether the dye is given by mouth or intravenously. Persistence of the shadow after a fatty meal is indicative of a pathologic condition of the gallbladder. In comparison with a positive clinical history and a positive cholecystogram, the icterus index, the qualitative and quantitative van den Bergh tests, duodenal drainage and fractional analysis of the gastric contents are only of secondary importance in the diagnostic armamentarium.

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[13] Rose, C. B.: Some Problems and Results in Cholecystography, Radiology **22**:197-201 (Feb.) 1934.

[14] Ferguson, A. N., and Palmer, W. L.: Cholecystography: Its Clinical Evaluation; Study of Two Thousand and Seventy Cases, J. A. M. A. **100**:809-812 (March 18) 1933.

[15] Burden, V. G.: X-Ray Gall Bladder: Surgical Opinion, Am. J. Surg. **22**:60-63 (Oct.) 1933.

[16] Moore, S.: Cholecystography: Analysis After Six and One-Half Years' Application, J. A. M. A. **95**:1957-1961 (Dec. 27) 1930.

[17] Clute, H. M., and Swinton, N. W.: Management of Gallstones: Review of Two Years' Experience, S. Clin. North America **14**:1137-1145 (Oct.) 1934.

A glance at table 4 shows that in our group of 133 patients cholecystographic studies were done on 58. The cholecystographic picture was correct, as far as disease of the gallbladder other than stone is concerned, in 82.7 per cent. The diagnosis as to the presence or absence of stone was made correctly by the cholecystogram in only 51.7 per cent of the patients studied. The latter results may be explained by the fact that about 60 per cent of biliary calculi are radiolucent and are therefore not visualized by the cholecystogram. Flat roentgenograms were made of only 8 patients, with a 50 per cent correct diagnosis for the presence or absence of stone.

TABLE 4.—*Correlation of Cholecystogram and Flat Roentgenogram with the Operative and Pathologic Pictures*

	Absence of Stone*		Presence of Stone†	
Roentgenographic Picture	No.	Pathologic Picture	Chronic Chole-cystitis	Acute Chole-cystitis
Cholecystogram				
Reported normal	2	Chronic cholecystitis	3	1
Nonfilling or poor filling with stone	*2*	*Chronic cholecystitis without stone*	*19*	*1*
Nonfilling or poor filling without stone	5	Chronic (4 cases), congested (1 case)	18	3
Normal filling with no shadows	1	Chronic	3	0
Flat roentgenogram				
Evidence of stone	1	Subchronic, no stones	2	2
No evidence of stones	0		3	0

* Roentgenographic studies were made on 11 of 15 patients without stone.
† Roentgenographic studies were made on 55 of 118 patients with stone.

3. Laboratory studies are of some diagnostic importance. In spite of the great amount of work that has been done in studying the functions and chemistry of the liver, investigators are still in the dark when they try to evaluate the state of hepatic function in a particular case. The various dye tests and the galactose tolerance test are of some value in estimating some of the functions of the liver but are insufficient to answer the question as to what will be the physiologic response of the liver in a given case in the event that a laparotomy is performed.

Fowler[18] said that in 80 of 100 patients with disease of the gallbladder the symptoms subside or can be successfully treated medically, but he is contradicted by his own statistics, which cover a study of 979 patients. His figures show that a higher mortality and morbidity and failure to obtain relief from symptoms occur in patients who are treated medically for a long time, in whom pathologic processes pursuant to the disease of the gallbladder are allowed to develop. The greatest factor in deaths from disease of the biliary tract appears to be the delayed operation, which permits of the development of the train of physiologic and pathologic changes that occur with the passing of time.[19] It must be remembered that disease of the gallbladder often affects other surrounding organs[20] besides the liver, frequently causing chronic pylorospasm, pancreatitis and possibly cardiac[21] and renal derangement. Lahey has well said "our medical friends must overcome the complacency with which they permit patients to go through repeated attacks of gall-stone colic" (quoted by Palmer[19a]).

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[18] Fowler, R. S.: Gall Bladder Disease: One Thousand End Results, Am. J. Surg. 22:53-59 (Oct.) 1933.

Goldish and Gillespie[22] showed that the average age of the patients who have died after operation for disease of the gallbladder is 10.3 years greater than that of those who lived. Heuer[23] concluded that the difficulties which beset the surgeon during and after the operation are the results of prolonged disease. The deeply jaundiced patient with obstruction of the common duct, lowered vitality, poor resistance to infection, renal damage and a tendency to hemorrhage presents an example of the result of prolonged disease; such a patient will die all too frequently notwithstanding the best surgical measures.

Of the 9 patients who died after operation (table 5), 7 were women, ranging in ages from 45 to 64 years; 5 gave a history of symptoms relative to the gallbladder extending over five years and 2 over ten years. Although none of these deaths definitely fall into any of the three groups of "liver deaths" as described by Heyd,[24] the liver showed pathologic changes, severe in many instances, in all of the cases in which autopsy was performed. Multiple abscesses of the liver were found in 5 of the 8 patients on whom autopsy was performed, and hepatitis of varying severity was found in 7. All of the 9 with a history of prolonged involvement of the gallbladder showed evidence also of involvement of the pericholecystic structures, the liver, pancreas or kidneys or

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[19] (*a*) Palmer, D. W.: Preoperative Pathology in Its Relation to Post-Operative Gallbladder Deaths, Ohio State M. J. **30**:293-297 (May) 1934. (*b*) Pratt, G. H.: Cholecystectomy and Cholecystostomy in Acute Suppurative and Gangrenous Cholecystitis, Am. J. Surg. **22**:46-52 (Oct.) 1933. (*c*) Bashein.[11]

[20] Mason, J. T., and Blackford, J. M.: Conservative Treatment of Cholecystitis, J. A. M. A. **99**:891-893 (Sept. 10) 1932.

[21] Schwartz, M., and Herman, A.: Association of Cholecystitis with Cardiac Affections: Study Based on One Hundred and Nine Cases, Ann. Int. Med. **4**:783-794 (Jan.) 1931.

[22] Goldish, D. R., and Gillespie, M. G.: Review of Three Hundred and Forty-Seven Gall Bladder Operations, Am. J. Surg. **21**:30-37 (July) 1933.

[23] Heuer, G. J.: Factors Leading to Death in Operations upon Gall Bladder and Bile Ducts, Ann. Surg. **99**:881-892 (June) 1934.

[24] Heyd, C. G.: Liver Deaths in Surgery of Gallbladder, J. A. M. A. **97**: 1847-1848 (Dec. 19) 1931.

TABLE 5.—*Analysis of Cases of Cholecystitis in Which Death Occurred After Cholecystectomy and Cholecystostomy*

Case No.	Patient	Age	Sex	Duration and Symptoms	Period Covered by Past History	Period Before Operation	Operation	Operative Findings	Clinical Course	Time of Death After Operation	Necropsy
1	A.B.	46	F	5 days; jaundice; colic	6 yr.	7 days	Cholecystostomy	Acute ulcerative calculous cholecystitis; stone in cystic duct; abscess of gallbladder bed	Paralytic ileus	3 days	Acute ulcerative cholecystitis; abscesses of liver; localized peritonitis; fatty infiltration of pancreas
2	M.D.	64	F	1 mo.; colic and dyspepsia	12 yr.	1 day	Cholecystostomy	Shrunken gallbladder; many stones; stone in cystic duct; hepatitis; adhesions	Septicemia; positive blood culture	4 days	Chronic cholecystitis; abscesses of liver; localized peritonitis; periportal cirrhosis
3	R.S.	55	F	3 wk.; jaundice; colic; dyspepsia	12 yr.	10 hr.	Cholecystectomy; choledocholithectomy	Gangrenous cholecystitis; stone in common bile duct; adhesions	Severe postoperative shock; hematemesis	5 days	Subchronic exacerbation of focal necrosis; abscesses of liver; infarction of liver; portal cirrhosis
4	A.G.	40	M	10 days; chills; fever; jaundice	6 yr.	6 days	Cholecystectomy; appendectomy	Chronic calculous cholecystitis; appendical abscess	Chills, fever and intestinal obstruction	47 days	Suppurative pylephlebitis of portal vein; abscesses of liver; gangrene of small intestines
5	E.B.	46	F	2 wk.; qualitative dyspepsia	7 yr.	1 day	Cholecystectomy	Chronic cholecystitis; adhesions	Intestinal obstruction due to adhesions	3 days	Chronic cholecystitis; adhesions producing obstruction; postoperative shock; fatty infiltration of liver and pancreas
6	P.B.	48	F	4 days; vomiting; fever; uremia	5 yr.	7 days	Cholecystectomy	Chronic calculous cholecystitis	Abdominal distention; pulmonary atelectasis	13 days	Multiple hemorrhagic areas; necrosis and hepatitis; purulent bronchitis
7	B.M.	45	F	2 mo.; chills; fever; jaundice; colic	5 yr.	37 days	Cholecystectomy; choledochotomy	Chronic calculous cholecystitis; pericholecystic adhesions; induration of liver and pancreas	Hematemesis; melena; hemorrhage from operative site	20 days	Secondary hemorrhage from operative site; diffuse hepatitis; abscesses of kidneys
8	A.J.	60	F	3 mo.; colic; qualitative dyspepsia	10 yr.	26 days	Cholecystectomy	Acute exacerbation; chronic calculous cholecystitis; pericholecystic adhesions	Circulatory collapse; laparotomy showed no hemorrhage	1 day	No necropsy
9	J.F.	35	M	1 day; fever; colic	0	10 hr.	Cholecystostomy	Acute gangrenous calculous cholecystitis	Abdominal distention; anuria; uremia on third day after operation	7 days	Uremia; gangrenous cholecystitis; local peritonitis; adhesions; portal cirrhosis; fatty infiltration of pancreas; congenital aplasia of right kidney; toxic nephrosis

combinations of these organs. The presence of adhesions in 6 of these patients made operation more difficult. In case 5 the many adhesions present caused intestinal obstruction and finally death. The patient in case 2 died of septicemia, which undoubtedly was present but unrecognized prior to operation. A blood culture taken on the day after the operation was positive for Friedländer's bacillus. Case 4 should not really be listed under "gallbladder death," although the history pointed to disease of the biliary tract. Operation in this case revealed besides chronic calculous cholecystitis, an appendical abscess in which the appendix had sloughed off. Suppurative pylephlebitis with multiple abscesses of the liver and infarction and gangrene of several feet of small intestine developed, and the patient died. In case 9 anuria developed within twenty-four hours postoperatively, and the patient died six days later of uremia. This case might be regarded as an example of the "hepatorenal" syndrome described by Schutz and his co-workers.[25]

COMMENT AND SUMMARY

We have presented a clinical and pathologic review of disease of the gallbladder in 133 patients who were operated on at the Mount Sinai Hospital from 1930 to 1935. Of this group, we have been able to obtain informative follow-up data on 83 persons. Although our group is too small to permit drawing definite conclusions regarding any single phase of disease of the gallbladder and its treatment, nevertheless, we feel that we are justified in stressing the following observations:

1. The clinical history of biliary colic, and to a lesser extent of qualitative dyspepsia for fried and fatty foods and of jaundice, is of primary importance in the establishment of a diagnosis of disease of the biliary tract. Of the clinical tests, the cholecystographic study is the most important, and in our series of 58 cases a correct diagnosis was made in 82.7 per cent.

2. The results of cholecystectomy on patients with noncalculous cholecystitis were better when the patient presented a definite history of biliary colic and a definite pathologic process was found at operation. Cholecystectomy on patients with noncalculous cholecystitis in whom the pathologic process was minimal and the clinical history of biliary colic was not definite resulted in relief of symptoms in only about 56 per cent as compared to cure or great improvement in 67 per cent of those giving a definite history of biliary colic.

3. Our follow-up data on 63 patients with calculous cholecystitis showed that the clinical results are far better in those with stone than

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[25] Schutz, C. B.; Helwig, F. C., and Kuhn, H. P.: Contribution to Study of So-Called Liver Deaths, J. A. M. A. **99**:633-636 (Aug. 20) 1932.

in those without stone. Of the 63 patients about whom information was obtained, 62 were either cured or greatly improved, a percentage of 98.4 as compared to the 63.2 per cent of the noncalculous group.

4. The results following cholecystectomy on 22 patients with acute cholecystitis included in our group with calculous cholecystitis indicate that a radical operation as soon as the patient has been adequately prepared is the desirable mode of treatment. Of the 22 patients presenting acute gangrenous, acute ulcerative or an acute exacerbation of chronic cholecystitis, only 1 died after operation. Both the morbidity and the mortality in the cases of acute cholecystitis were less after cholecystectomy than after cholecystostomy.

5. Our review of disease of the biliary tract in 133 patients has shown that there is a direct relationship between the duration and the severity of the clinical symptoms, the morbidity and mortality and the character of the pathologic lesions noted at operation and at necropsy. The significant part which the pericholecystic complications, the result of prolonged medical treatment for disease of the gallbladder, played in the fatal outcome of the 9 patients justifies a plea for early operative treatment of patients suffering with disease of the biliary tract after a definite diagnosis has once been established.

Drs. B. Lipshutz, M. Behrend and E. L. Eliason granted permission for the inclusion of their cases in this report.

CARCINOMA OF THE SUPRAPAPILLARY PORTION OF THE DUODENUM

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The purpose of this communication is to report six cases of carcinoma of the suprapapillary segment of the duodenum and to analyze and summarize the data obtained from the reported cases of this condition. Reports of one hundred and four cases were abstracted from the literature, thirty-five[1] of which were regarded as acceptable on the basis of the data presented, a clinical history and gross and microscopic studies of the primary lesion being presented in each report. Twelve[2] additional cases, although probably authentic examples of this condition, could not be included in the present analysis because of insufficient clinical or pathologic data. Fifty-seven more reported cases were discarded, nineteen because, owing to involvement of the stomach, pancreas or bile passages in the malignant process,[3] the duodenal origin of the lesion was not established with certainty and thirty-eight[4] because the histologic

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From the Pathological Laboratories of the Jefferson Medical College and Hospital, the Jefferson Hospital Tumor Clinic and the Philadelphia General Hospital.

[1] Coupland; Ewald; Montgomery and Sherman; Pic (case 1); Letulle; Aaron; Gerster; Geiser (case 1); Bibby and Stewart; Jefferson; McGuire and Cornish (case 3); Herman and von Glahn; Ramond, Vincent and Clémont (case 1); Van Tienhoven (case 2); Morrison and Feldman; Dewis and Morse (cases 1, 2, 3, 4 and 5); Kettle; Archibald; Pacetto; Lageder; Meyer and Rosenberg (case 2); Mateer and Hartman (case 1); Rutishauser (cases 1 and 5); Cave (cases 8 and 11); Eger (case 1); Lisa; Levine and Fitzhugh (case 2); Dardinski; Ochsner and Wilbur (case 2); von Hrabovsky (case 2); Doub and Jones (case 1—the same as reported by Mateer and Hartman, case 1); McNamara, and Bastos.

[2] Geiser (case 4); Peck; Reichel and Staemmler (cases 2 and 3); Borrmann (cases 1 and 2); Arisz (cases 1 and 2); Raiford (cases 46597 and G 662); Bookman; Schüssler (case 1) and Rutishauser (case 4).

[3] Fullet; Drechsler; Béringier; Coupland; Höft; Trémolières; Geiser (case 9); Benedict; Bassler and Grant; Lichty (cases 1 and 3); Judd (case 2); Orator (cases 1 and 2); Cabot (case 15111); Hinton (cases 1 and 3); Popovici, and Wilson and Noble.

[4] Haley; Carrer; Dickinson; Cayla; Boyé; Whittier (case 12); Pye-Smith; Weecke; Perry and Shaw; Pic (case 2); Günther; Czygan; Heynen; Wurm

(Footnote continued on next page)

studies were not reported, the diagnosis apparently having been made on the basis of gross examination alone. Of historical interest are the cases reported by Hamberger (1746) and Morgagni (1761).

REPORT OF CASES

CASE 1.—J. P., a white man aged 35, whose complaints were belching, vomiting, anorexia and a loss of 30 pounds (13.6 Kg.) in weight, was admitted to the Jefferson Hospital on March 22, 1931, with the clinical diagnosis of carcinoma of the head of the pancreas. For years he had been troubled with gas and belching. In November 1929 he experienced a brief attack of severe epigastric pain, which was followed a week later by jaundice. At operation on Jan. 2, 1930, in another hospital, a markedly thickened gallbladder containing many stones was removed, together with several drachms of gravel from the common bile duct, which was incised and drained. Jaundice did not entirely disappear owing to obstruction at the ampulla of Vater, and the drainage tube could not be removed from the common duct. A choledochogastrostomy stoma was then established, and the jaundice cleared entirely, the patient remaining practically free from symptoms until February 1931. Again jaundice recurred, associated with vomiting, excessive gas and pain in the right upper abdominal quadrant, and the patient was admitted to the Jefferson Hospital on March 22.

Physical examination revealed tenderness in the right upper abdominal quadrant and a palpable mass, which descended with inspiration. The hemoglobin content of the blood was 27 per cent, the red cell count 1,280,000, the white cell count 1,100 and the color index 1.01. There were polychromasia and stippling, with many microcytes, macrocytes and poikilocytes. The urine was alkaline, contained albumin and had a high specific gravity varying from 1.016 to 1.030. The stools contained blood and an excessive amount of fat. There were blood and bile in the vomitus, which showed a free acidity of 18 and a total acidity of 28. A roentgenogram of the gastro-intestinal tract was unsatisfactory because of considerable retention of food. With treatment the hemoglobin content increased to 43 per cent, the red cells to 2,850,000 and the white cells to 8,200. At laparotomy on April 14, local anesthesia being used, the stomach appeared pale and distended and the jejunum pale and collapsed. On account of dense adhesions it was not possible to make a satisfactory examination of the duodenum and bile ducts. A large, irregular, firm, slightly tender mass, 7.7 cm. in diameter, was palpated in the retroperitoneal region, and a posterior gastro-enterostomy was performed in the usual manner. That night there was slight oozing of blood from the wound, the patient was markedly dehydrated, the chloride content of the blood was 406.9 and the carbon dioxide-combining power rose from 98 to 128. Fluids were administered subcutaneously and intravenously, and a small transfusion of blood was given. The following evening the pulse became rapid and the temperature high, and there was a marked drop in the blood pressure. The patient died from hemorrhage on March 17.

Autopsy was performed four hours after death. The combined gross anatomic and microscopic diagnoses were: (1) annular constricting adenocarcinoma of the

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(cases 1 and 2); Friedrich (cases 1 and 2); Moynihan (cases 1 and 2); George and Leonard; Helm; Judd (cases 1, 3, 4 and 5); McGuire and Cornish (case 4); Vervloet; Eusterman; Berkman and Swan (cases 1, 2, 3, 4, 5 and 6); Brüning; Dewis and Morse (cases 8 and B); Hanganutz, and Brdiczka.

suprapapillary portion of the duodenum with constriction of the common bile duct and extension and metastases to the pancreas, regional lymph nodes and surrounding tissues; (2) hydrohepatosis with marked jaundice; (3) chronic interstitial pancreatitis; (4) recent gastro-enterostomy; (5) peritoneal, pericardial and bilateral pleural effusions, and (6) pulmonary edema and congestion.

Dense fibrous adhesions passed between the fossa of the gallbladder and the lower end of the stomach and duodenum, including the inferior margin of the liver, which was adherent to the anterior abdominal wall. The lumen of the duodenum just proximal to the ampulla was practically completely obliterated by an annular constricting lesion. The mucous membrane in this area appeared thickened and nodular but apparently was not ulcerated. There was marked neoplastic induration of the wall of the duodenum, with direct extension into the pancreas and the surrounding tissue.

The proximal portion of the duodenum and stomach were greatly distended, and the pyloric ring was completely effaced. The lower border of the stomach extended below the umbilicus; its mucosa was atrophic, and its lumen contained bile-stained, bloody fluid. The margins of the gastro-enterostomy opening were intact but swollen and edematous. A choledochogastrostomy opening did not exist, and there was no gallbladder. The lower end of the common bile duct was buried in a mass of adhesions and cancer tissue. A probe was passed with difficulty through the ampulla of Vater into the common bile duct, which was markedly thickened and dilated. The liver was irregular on the surface, and the capsule was thickened and covered with dense adhesions, especially on the under-surface. On section the hepatic tissue was dark greenish brown, the normal markings were absent, there was a good deal of fine fibrosis and the intrahepatic ducts were markedly thickened. Many of the mesenteric, peripancreatic, retroperitoneal and periaortic lymph nodes were enlarged, firm and gray, measuring from 2 to 3 cm. in diameter.

Sections from the constricting lesion in the duodenum showed the mucous membrane to be markedly thickened (fig. 1) and interspersed with large areas of atypical epithelium. Brunner's glands formed a thick, practically continuous submucosal layer. Malignant transformation appeared to occur first in the deeper parts of the mucosa, where the cells became irregular in shape, often rounded, and were closely packed instead of forming crypts. For a space they seemed to respect the muscularis mucosa, penetrating it only in limited small areas. These cells permeated through Brunner's glands (fig. 2), tending to follow the supporting stroma, and on reaching the submucosal areolar tissue spread out laterally almost the entire length of the sections. They infiltrated in and between the muscle bundles, usually at right angles to the length of the section, and were seen deep to the muscle (fig. 3). One large nerve was invaded, and epithelial cells were seen in small veins, arteries and lymphatics. In places the cells formed small acini of cuboidal or columnar cells, but elsewhere there was no characteristic arrangement, the cells being in dense clumps or in slender strands separated by fibrous tissue. The individual cells were variable in size and shape but usually small, with round and ovoid hyperchromatic nuclei, which were sometimes marginal and crescent shaped, giving the cell a signet ring appearance. No mitotic figures were seen. The fibrous stroma was scant in the mucosa but more abundant deep in the wall of the duodenum.

There were marked atrophy and fibrosis of the pancreas within and about the lobules. Lymphocytes were scattered throughout and tended to clump about the ducts, nerves and infiltrating strands of atypical epithelial cells. The tumor

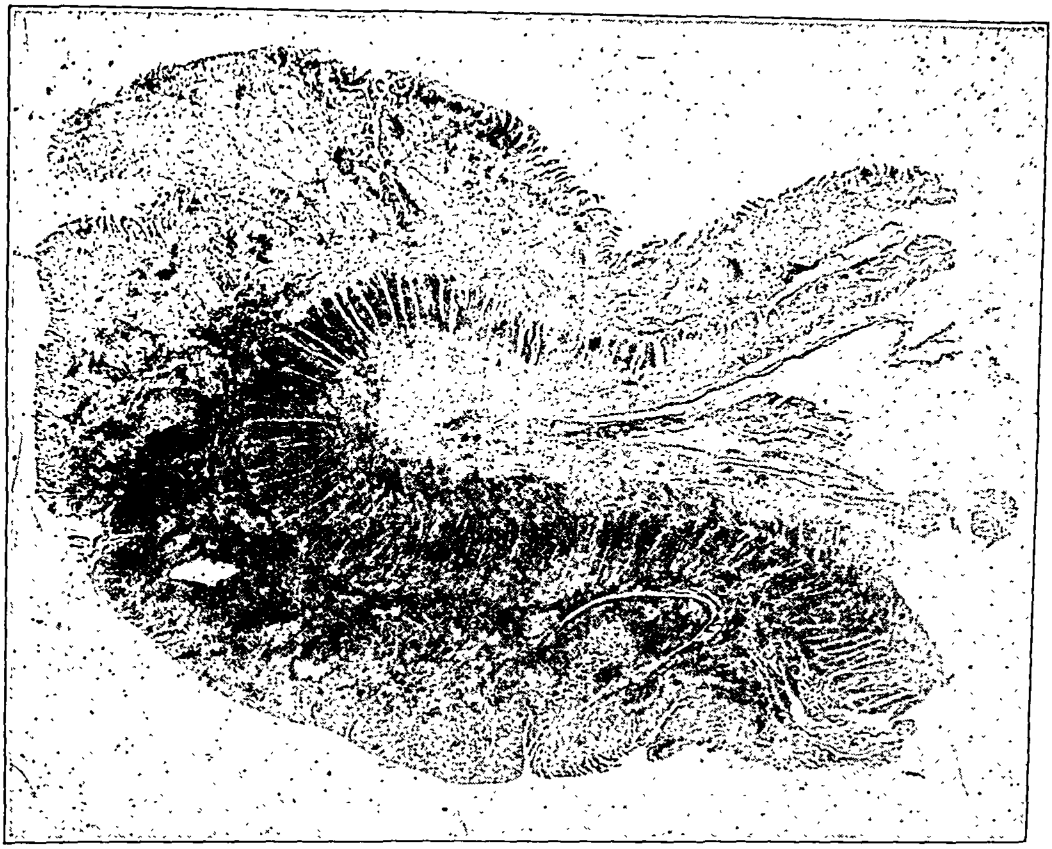

Fig. 1 (case 1).—Section from the constricting lesion in the duodenum, showing marked neoplastic thickening of the mucous membrane; circa × 7.

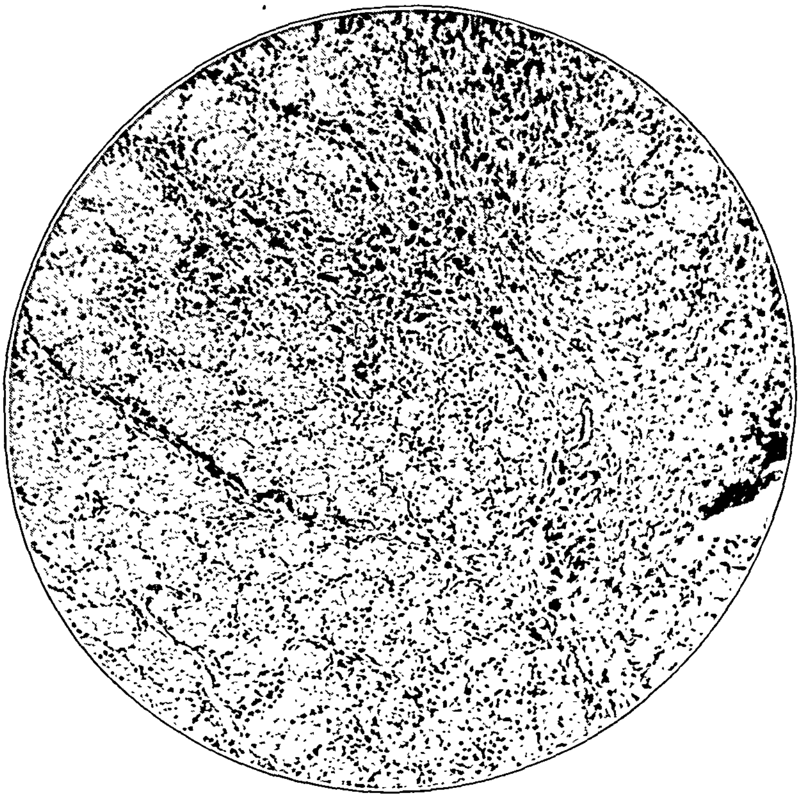

Fig. 2 (case 1).—Section of the duodenal lesion showing neoplastic permeation of Brunner's glands; × 100.

tissue here had a more abundant stroma than in the intestine and was frequently observed surrounding nerves and vessels.

Sections of a lymph node showed almost complete replacement by a dense mass of undifferentiated epithelial cells with little stroma, the atypical appearance of the cells being a striking feature.

The liver presented the characteristic picture of biliary stasis, with granules and droplets of bile pigment, bile casts and degeneration and necrosis in the inner third of the lobule. The sinusoids were dilated, the small bile ducts were proliferated and there was a marked increase in periportal connective tissue, which frequently completely encapsulated the lobules. Scattered throughout the sections were numerous focal midzonal and biliary necroses, which were often converted into small abscesses.

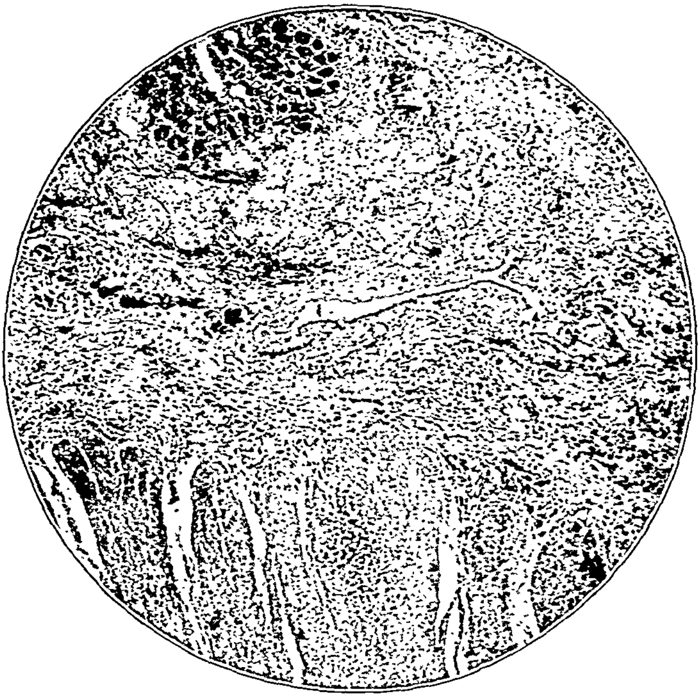

Fig. 3 (case 1).—Section of the duodenum showing a small strip of mucous membrane, Brunner's glands and the underlying muscle. The neoplastic cells have permeated the connective tissue stroma of Brunner's glands and have infiltrated in and between the muscle bundles frequently at right angles to the length of the section; × 50.

Case 2.—C. N., a white man aged 69, whose complaints were vomiting, constipation, abdominal distress and marked thirst of two weeks' duration, was admitted to the hospital on Jan. 30, 1924, with the clinical diagnosis of carcinoma of the pancreas. During the preceding half year he lost 15 pounds (6.8 Kg.) in weight. The onset of the terminal illness occurred suddenly one evening on Jan. 13, 1923, with the vomiting of a large quantity of light frothy material, unassociated with pain or nausea. The patient returned to work the following day but vomited that night after the evening meal and on each succeeding night for a week. At first the vomiting was not forceful, but later he had to support his abdomen because of retching. There were tarry stools, slight constipation, a good deal of belching with the attacks of vomiting and frequent eructations of sour fluid. On physical examination the epigastric region was distended and slightly rigid but not tender, and no definite mass was visible or palpable. There were a marked grade of secondary anemia and a leukocytosis of 22,600. The urine had a specific gravity of from 1.017 to 1.025 and contained albumin and casts. The stools contained blood. The gastric content showed a residual total acidity of 34 and free hydrochloric acid of 19; after a test meal these figures gradually rose to a maximum of 49 and 30, respectively, at the end of two hours. Four days after admission the patient fainted after vomiting 100 cc. of thick dark brown material. He regained consciousness after a short interval but was weak, cold and restless and complained of severe pain in the lower part of the abdomen. That night he vomited 250 cc. of bright red blood and died five minutes later.

Autopsy was performed thirteen hours after death. The combined gross anatomic and microscopic diagnoses were: (1) adenocarcinoma of the suprapapillary segment of the duodenum, with extension to the pancreas and metastasis to the liver and peritoneum; (2) duodenal hemorrhage; (3) hemoperitoneum; (4) pulmonary emphysema, congestion and edema; (5) arteriosclerosis of the aorta and renal arteries; (6) chronic nephritis, and (7) fibrosis and degeneration of the myocardium.

In the duodenum just distal to the pylorus was a soft dark reddish green ulcer, 3 by 5 cm., which completely encircled the intestine. The wall of the duodenum was composed of firm gray tissue, which extended laterally in the muscular coat beneath the pyloric ring into the wall of the stomach for 2 cm. The duodenum at the site of the ulcer was bound to the head of the pancreas, which was infiltrated by a tumor mass, 1.5 cm. in diameter, continuous with the lesion in the duodenum. The distal aspect of the duodenal lesion was sharply limited by normal mucosa. The stomach and esophagus were distended with blood. The peritoneum contained several firm gray nodules, measuring from 1 to 3 mm. in diameter, on the under-surface of the diaphragm and in the visceral serosa of the small and large intestine.

The liver weighed 2,080 Gm. and was reddish brown and soft. There were many circumscribed firm gray nodules, averaging 2 cm. in diameter, which formed a large confluent mass in the edge of the right lobe. The largest of these nodules showed necrotic centers, while those on the surface were regularly umbilicated. The biliary passages were patent.

There were bilateral congestion and edema of the lungs and several small, firm, discrete, pearly gray subpleural nodules.

Histologic sections of the duodenal lesion disclosed a transition from normal mucous membrane into a large area of atypical epithelial cells showing extensive necrosis and hemorrhage. Lateral to the area of ulceration Brunner's glands were hyperplastic, but immediately underneath it they were destroyed by the cancer tissue, which permeated the stroma of these structures. The tumor cells penetrated through all coats of the intestine and spread out laterally into the surrounding fat along the peritoneal surface. The cells were discretely arranged, large, round or oval elements with acidophilic or basophilic vacuolated cytoplasm and relatively small oval or sickle-shaped hyperchromatic nuclei, which were often eccentrically situated. Other nuclei were large and pale with multiple lobulations and occupied a more central position in the cell. Mitotic figures were rare. A large amount of stringy mucinous material was present between the cells and in the cytoplasmic vacuoles. The tumor cells were further separated into nests and linear masses by strands of avascular connective tissue infiltrated with small round cells. In the depths of the main tumor a few acini lined with cuboidal and columnar cells were observed, and many large blood vessels contained tumor cells.

The large tumor nodules in the liver showed extensive hemorrhage and necrosis. The atypical epithelial cells grew in solid nests in some places, but mainly they were desquamated into small alveolar spaces enmeshed in stringy mucinous material. As a rule the cells had an abundance of finely vacuolated cytoplasm, which contained droplets of mucin. Many nuclei were oval and eccentrically placed in the cell, while others were large, irregular and hyperchromatic. The stroma was abundant and hyalinized.

In the under-surface of the diaphragm the tumor cells formed nests and acini supported by dense connective tissue stroma, and there was little tendency to extend below the serosal surface.

CASE 3.—M. C., a physician aged 58, a morphine addict, was admitted to the hospital in a moribund condition on April 15, 1916. A few days previously he had been picked up unconscious from the floor of his home and put to bed by an attendant, who reported that the patient had subsequently passed large quantities of blood by bowel. Because of his stupor and delirium it was difficult to make a satisfactory physical examination during the period of hospitalization, and the findings contained in the clinical record were of little significance with regard to the lesions disclosed at autopsy. It was observed that the patient passed blood by bowel several times. The urine was acid, contained hyaline casts and had a specific gravity of 1.016. The hemoglobin content was 29 per cent, the red cell count 1,880,000, the white cell count 11,600 and the color index 0.8. The patient died two days after admission without regaining consciousness.

Autopsy was performed thirteen hours after death. The combined gross anatomic and microscopic diagnoses were: (1) papillary scirrhous adenocarcinoma of the first portion of the duodenum, with metastasis to the liver and peritoneum; (2) hemorrhage into the intestinal tract; (3) calculous cholecystitis; (4) sclerosis of the aortic and mitral valves; (5) arteriosclerosis of the aorta; (6) acute degeneration of the myocardium and kidneys; (7) cerebral and pulmonary edema, and (8) a small hemorrhagic peritoneal effusion.

An annular ulcer, 5 cm. in diameter, was found in the first portion of the duodenum immediately adjacent to the pyloric sphincter. The edges were hard, indurated and sharply outlined, while the floor was irregular and nodular and contained a small thrombosed vessel. The wall of the duodenum opposite the ulcer was adherent to the neck of the gallbladder. The stomach was markedly dilated, while the remainder of the bowel was dilated and filled with black material.

The peritoneal cavity contained a small amount of blood-tinged fluid. The serosa was smooth, moist and glistening, except for a few small irregular neoplastic nodules on the under-surface of the diaphragm and the right pelvic wall.

The liver was large, soft and pale and contained many firm gray nodules, measuring from 1 to 4 cm. in diameter. The gallbladder was adherent to the wall of the duodenum and the lumen contained 25 cc. of viscid yellow bile and three small faceted calculi.

Microscopic sections of the duodenum disclosed a transition from normal mucosa to an ulcerated neoplastic lesion infiltrating laterally along the submucosa and extending deeply through the muscular wall to invade the peritoneum and superficial fatty tissue. The tumor cells were usually cuboidal or columnar, but many showed marked variation in size and staining with from one to several hyperchromatic nuclei. A few were observed in mitosis. The cells grew in small nests of imperfect strands but tended generally to reduplicate simple or papillary acinous structures and showed necrosis in many areas. The stroma was abundant, consisting of compact strands of collagenous fibers with a few young and old fibroblasts but not many blood vessels. There was a marked inflammatory reaction consisting of lymphocytes, chiefly limited to the muscular coats along the line of penetration of the tumor cells.

In the liver the atypical epithelial cells appeared to grow along the sinusoids and within the spaces remaining after absorption of necrotic hepatic cells.

CASE 4.—A. W., a white woman aged 85, was admitted to the Philadelphia General Hospital on March 29, 1929, with the clinical diagnosis of chronic intestinal obstruction. According to the clinical record, she had a stroke of apoplexy five years previously followed by impairment of the mental faculties. The terminal illness apparently began in January 1929, with black feces, vomiting and anal pain, both the vomitus and the feces being black. About the middle of March she became bedfast and refused all food; the vomiting continued, and there were no bowel movements until she entered the hospital two weeks later. On physical examination no noteworthy findings were recorded except that the tissues were dehydrated and râles were heard over the thorax. Death occurred suddenly on March 30.

Autopsy was performed twelve hours after death. The combined gross anatomic and microscopic diagnoses were: (1) obstructing primary scirrhous adenocarcinoma of the suprapapillary portion of the duodenum with extension and metastases to the pancreas, the liver and the wall of the gallbladder; (2) calculous cholecystitis; (3) chronic pancreatitis with fatty infiltration; (4) arteriosclerosis of the aorta and the coronary and renal arteries with chronic nephritis, and (5) pulmonary congestion.

The lumen of the duodenum 5 cm. distal to the pylorus was narrowed by a round elevated, indurated ulcer, 2 cm. in diameter. The entire intestinal wall immediately subjacent was firm, indurated, grayish white and adherent both to the pancreas and to the gallbladder. There were no appearances suggesting pancreatic invasion. The gallbladder was contracted about several small faceted greenish yellow concretions together with a small amount of dark grumous bile. On the peritoneal surface near the fundus were two or three small round, grayish white nodules. Its wall was considerably thickened, especially in the region of the neck, which was involved by masses of tumor tissue in the duodenum and liver. The liver weighed 1,120 Gm.; it was firm, and its capsule was thickened; a few grayish white nodules with central yellowish necrotic areas were scattered through the parenchyma. The quadrate lobe was practically entirely replaced by tumor tissue and was densely adherent to the immediately contiguous upper portion of the gallbladder. It was not possible to determine at autopsy whether the tumor arose primarily in the gallbladder, liver or duodenum, but the probabilities were stated in that order, the duodenum being considered the least likely primary site.

The stomach was markedly dilated, and its outline resembled the curve of a fish-hook with the lower border almost at the symphysis pubis. The walls of the stomach were hypertrophied, and the rugae were absent. The body tissues were not jaundiced, and there was no evident obstruction of the biliary passages.

Microscopic sections of the duodenum showed a pale-staining, partially autolyzed mucous membrane, which merged abruptly with an ulcerated area covered with atypical epithelial cells. The area of ulceration remained comparatively superficial and did not extend below the deep portion of the submucosa. All the coats of the duodenum, however, were involved by cancer tissue. Brunner's glands were completely absent from the area of ulceration but showed no abnormalities in the adjacent portion. The atypical epithelial cells penetrated through all coats of the duodenum and were distributed singly, in small clumps and nests, only rarely reduplicating acinous structures. The cells showed an extreme degree of irregularity in size, shape, staining and number of nuclei; most of them were polyhedral and spindle shaped, with relatively large nuclei and scanty acidophilic cytoplasm, which was usually granular and occasionally contained vacuoles. The cells lining the acinous structures were often cuboidal or columnar. Most of the nuclei were oval or indented and generally enlarged; many were distorted and hyperchromatic, while the largest ones were frequently lobulated, and a few contained inclusions. Only a few mitotic figures were observed. In the musculature tumor cells were observed in small spaces in nerves, and the walls of blood vessels and occasionally in their lumens.

The pancreas showed interstitial fibrosis, fatty infiltration and considerable autolysis. A small area of infiltrating neoplastic cells was noted in one of the large connective tissue septums.

In the liver, in contrast to the duodenum, the tumor cells were more regular, more frequently in mitosis, tended generally to reduplicate acinous structures and showed less supporting stroma. Several of the larger areas of tumor tissue contained central areas of necrosis.

The mucosa of the gallbladder was autolyzed, although the structural outlines of its stroma were well preserved and showed no involvement by tumor tissue. The wall in general and the peritoneal coat especially were markedly thickened, fibrotic and infiltrated with small round cells. The outer portion of the wall was invaded by small clumps of atypical epithelial cells, which stopped short of penetrating through to the mucous membrane.

Nothing was observed microscopically to suggest a cholecystic origin of the tumor. The contracted, thickened and fibrotic character of the gallbladder, together with the presence of biliary calculi and the contiguous relationship the gallbladder bore to the neoplastic lesions in the liver and duodenum, could readily suggest such an origin. A careful evaluation of the anatomic and histologic data warrants the conclusion, we believe, that the lesion under consideration was duodenal in origin. The tumor masses in the gallbladder can be accounted for by extension and metastasis, probably by way of local adhesions, the result of preexisting calculous cholecystitis.

Case 5.—I. T., an emaciated white woman aged 66, was admitted to the Philadelphia General Hospital on Oct. 21, 1923, with vomiting, loss of weight and weakness. There was a history of an operation for gallstones eight years previously and shortly after that one for "abscess of the stomach." Late in 1922 the patient began to complain of nausea, loss of weight and strength and a feeling of heaviness in the abdomen. In August of the next year frank epigastric pain developed, and the patient vomited constantly. There was no relationship between the taking of food and the onset of epigastric pain, and no blood was detected in the vomitus. On physical examination several nodules believed to lie in the deep fascia were felt in the abdominal wall, which was thin and doughy in consistency. The other resistant masses were palpated in the region of the stomach, the largest of these being 5 cm. in diameter. The patient's course in the hospital was characterized by restlessness, persistent vomiting and progressive weakness and stupor; death occurred on October 24.

Autopsy was performed twelve hours after death. The combined gross anatomic and microscopic diagnoses were: (1) papillary adenocarcinoma of the first portion of the duodenum with metastases to the liver and lungs and the mesenteric and peribronchial lymph nodes; (2) chronic interstitial pancreatitis; (3) arteriosclerosis of the renal arteries with chronic nephritis; (4) chronic adhesive pleuritis and pericarditis; (5) pulmonary edema, and (6) chronic interstitial myocarditis.

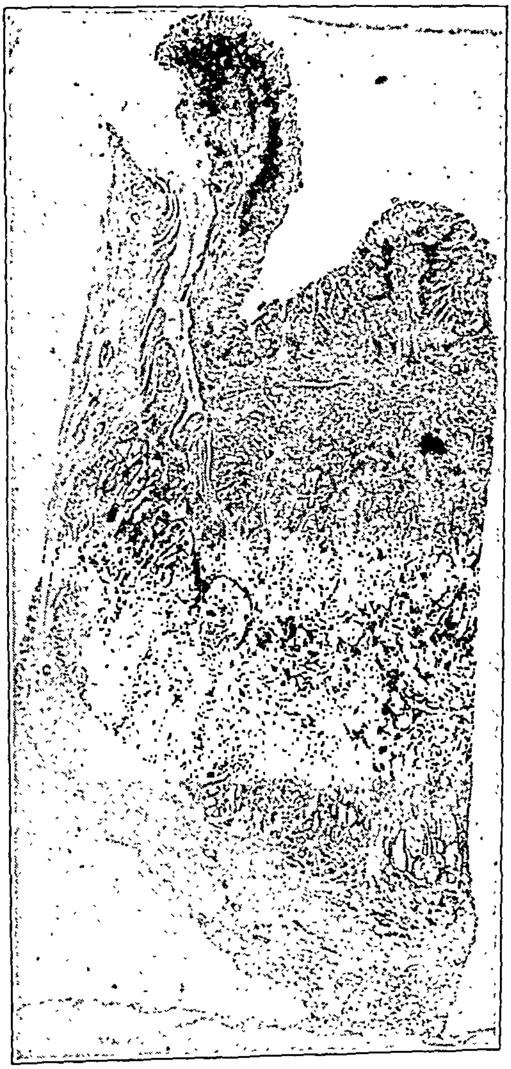

Fig. 4 (case 5).—Section of the duodenum showing hyperplastic changes in the muocus membrane and neoplastic involvement of all coats of the intestine; circa × 7.

The duodenum contained a small firm ulcer which measured 2 cm. in diameter and was located 5 cm. from the pylorus and 1 cm. proximal to the papilla of Vater. The margins of this lesion were elevated, indurated and thrown into folds over the central crater-like ulcer. Proximally the stomach and duodenum were dilated, and the wall of the latter was hypertrophied. The regional lymph nodes were enlarged and, with the head of the pancreas, were densely adherent to the wall of the duodenum opposite the primary lesion.

The liver was enlarged in its left lobe and contained many firm white, opaque nodules, measuring from 1 to 5 cm. in diameter. The gallbladder was absent, and the bile ducts were patulous.

Microscopic sections of the duodenum showed a transition from normal mucosa into a zone of hyperplastic and ultimately atypical epithelial cells with a papillary acinous arrangement (figs. 4 and 5). These cells penetrated all coats of the duodenum, including the serosa, which was thick and fibrotic. Brunner's glands were not very numerous and in several places were partially destroyed by invading tumor cells. The malignant transformation appeared to occur first in the superficial cells of the surface mucosa and gradually extended to involve the entire thickness of the mucous membrane, the crypts of the glands being involved last. The connective tissue stroma of the mucous membrane near the point of transition was thickened by infiltrating lymphocytes and plasma cells. Some glands were abnormally short, and others were dilated, long and tortuous. The acinous structures were coarse and irregular, with numerous large branches and ramifying cavities lined by from one to several layers of atypical epithelial cells. The lumens of these cystic structures varied in caliber; some contained papillary spurs which grew out perpendicular to the wall, while others were filled with viable or necrotic tumor cells or acidophilic detritus. The majority of the cells were tall columnar elements with rectangular nuclei, while others were

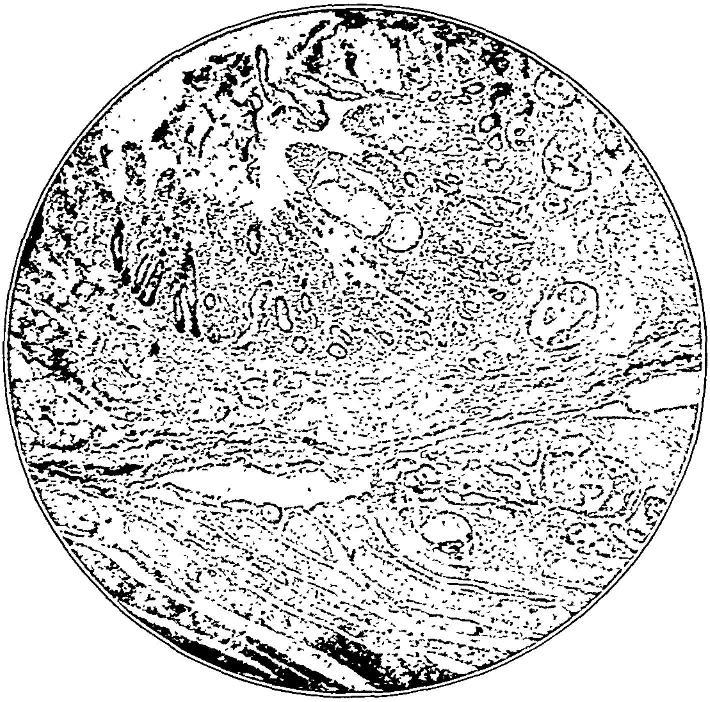

Fig. 5 (case 5).—Section of the duodenum showing a transition from normal mucosa into a zone of hyperplastic atypical epithelial cells with a papillary acinous arrangement. The tumor cells penetrate deeply into the submucosa and muscular coat; × 40.

cuboidal or flattened, and a few were greatly enlarged and polyhedral. The nuclei were pale and vesicular and usually situated near the base of the cell. A few were large, irregular and lobulated. Mitotic figures were present but not numerous. The cytoplasm of the atypical cells was abundant, deeply acidophilic and frequently contained single large vacuoles but little if any mucin. Extensive areas of necrosis were present throughout the tumor tissue. The stroma was loose, comparatively scanty and not very vascular. It was infiltrated with clumps of small round cells and leukocytes on the surface of the lesion and around the necrotic areas.

In the liver the tumor nodules were more solid and cellular, with less stroma and inconspicuous acinous and papillary formation.

Case 6.—E. H., a white man aged 44, entered the Philadelphia General Hospital on April 5, 1913, with gastric pain and jaundice. Pain began eight months previously, coming on after meals in association with belching, but later it assumed a hot burning character and became continuous. The patient was generally constipated and occasionally noticed gross evidence of blood in the stools. Jaundice developed several weeks before admission, but vomiting was never a symptom.

On physical examination jaundice was marked and emaciation extreme. There was fulness of the right upper quadrant, but the remainder of the abdomen was flat. The liver was felt 4.5 cm. below the costal margin, and the left lobe contained a few palpable nodules. Beneath the liver was a tense pear-shaped tumor mass, which moved with respiration.

The patient's course in the hospital was progressively downward. He began vomiting every day at first and finally almost hourly. The vomitus contained large quantities of fresh and of digested blood. An interesting observation was made at the end of the first week, when it was noted that the yellow color of the skin had lightened perceptibly and the gallbladder was barely palpable. The following day, however, the gallbladder became as large as it was formerly.

The urine was acid, had a specific gravity of 1.018 and contained bile. The red cell count was 2,600,000, the hemoglobin content 35 per cent and the leukocyte count 17,000. Blood was present in the feces. The vomitus was green and contained blood and hydrochloric acid. Death occurred on April 21.

Autopsy was performed forty-six hours after death. The combined gross anatomic and microscopic diagnoses were: (1) adenocarcinoma of the suprapapillary portion of the duodenum with extension to the pancreas and metastasis to the liver; (2) hydrohepatosis with marked jaundice; (3) chronic interstitial pancreatitis with extreme atrophy; (4) dilatation of the stomach; (5) hemorrhage into the stomach and intestines; (6) slight myocardial fibrosis; (7) congestion and edema of the lungs; (8) pulmonary anthracosis and emphysema, and (9) arteriosclerosis of the kidney with chronic nephritis and parenchymatous degeneration.

The first part of the duodenum was the seat of an extensive area of ulceration with ragged edges, about 5 cm. in diameter. Directly beneath this lesion was a firm white mass the size of a fist, involving the wall of the duodenum and the head of the pancreas. The remainder of the pancreas was small, white and firm, and the usual lobular appearance was indistinct. The stomach was greatly dilated and contained coffee-ground material. The intestines were distended with gas and bright red blood.

The liver measured 27 by 19 by 8 cm. and extended 3 fingerbreadths below the ribs. It was dark, olive green, tough and resistant to incision. A number of firm white nodules, measuring up to 3 cm. in diameter, were scattered through the parenchyma. On the surface the centers of these lesions were slightly depressed. The gallbladder was distended with thick bile, little of which could be expressed through the ampulla of Vater.

Microscopic sections of the duodenum showed all the coats infiltrated with masses of irregular tubules composed of a columnar type of cell lying in a framework of adult connective tissue. The stroma was abundant and infiltrated with round cells and polymorphonuclear leukocytes, especially in areas in which the tumor cells were necrotic. A few mitotic figures were observed.

ETIOLOGY

There is a considerable literature devoted to a discussion of the origin of carcinoma of the suprapapillary segment of the duodenum from duodenal polyps, accessory pancreatic tissue, misplaced remnants of gastric mucous membrane, simple ulcer, Brunner's glands and the minor papilla of Santorini. However, definite proof of any such etiologic relationship is lacking. Ochsner and Wilbur stated that in their case the minor papilla of Santorini was apparently the site of origin for the neoplasm. Although such an origin is possible, this view has yet to be substantiated.

The origin of the tumor from Brunner's gland was postulated in three cases (Ramond; Vincent and Clément; Pic, and Rutishauser's case 1). In the first two no evidence was presented to substantiate this point of view. Rutishauser, however, wrote at length regarding the fine histologic changes in Brunner's glands, which led him to believe that the tumor in his case originated in these structures. In view of the fact that the postmortem examination on Rutishauser's subject was held two days after death, these histologic details would appear to be of little value. These glands were described as hyperplastic in several other cases, but as they normally vary quantitatively in different areas of the suprapapillary segment of the duodenum, the significance of this observation is debatable. Morrison and Feldman noted that these glands were numerous in the vicinity of the carcinoma in their case but were correct in interpreting this feature on the basis that the tumor originated well up in the duodenum where the glands are normally numerous. In our cases Brunner's glands were frequently destroyed by marked inflammation, ulceration and neoplastic permeation of their stroma.

Most simple ulcers are located in the first 2.5 cm. of the duodenum, and it follows that if this condition is a precancerous lesion, carcinoma should occur rather commonly in this situation, and a proportionately large number should be confined to or at least border on this area. An analysis of this series does not support this hypothesis, for in the relatively few cases in which the lesion was situated above the papilla no significant difference could be established in its occurrence in any particular portion of the suprapapillary segment. After evaluating the evidence dealing with the association of simple ulcer and carcinoma, we are of the opinion that no proof exists to support the hypothesis that simple ulcer of the duodenum is a precancerous lesion.

AGE AND SEX; INCIDENCE

In the series of cases studied twenty-six of the patients were men (three Negroes), varying in age from 35 to 78, with an average age of about 57, and fifteen were women, varying in age from 23 to 85, with an average age of about 55.

Three of our six cases were discovered at the Jefferson Hospital in 3,526 autopsies and the others at the Philadelphia General Hospital, two between Jan. 1, 1920, and Dec. 31, 1935, 20,176 autopsies having been performed during that period.

ANATOMY

The suprapapillary portion of the duodenum extends from the pyloric sphincter to the papilla of Vater and includes, according to academic anatomy, the superior portion and the proximal part of the descending portion. The superior portion, commencing at the pylorus and measuring approximately 5 cm. in length, passes backward, upward and to the right, ending at the neck of the gallbladder. It is in relation above and in front with the quadrate lobe of the liver and the gallbladder, behind with the gastroduodenal artery, the common bile duct and the portal vein and below and behind with the head and the neck of the pancreas. The proximal descending portion, measuring from 3 to 5 cm. in length, extends from the neck of the gallbladder along the right side of the vertebral column to the papilla of Vater. It is in relation in front with the duodenal impression on the right lobe of the liver and the transverse colon; behind it has a variable relationship to the front of the right kidney in the neighborhood of the hilus; the renal vessels, the inferior vena cava and the psoas muscles below are also behind it; at its medial side are the head of the pancreas and the common bile duct; to its lateral side is the right colic flexure. The common bile duct and pancreatic duct together perforate the medial side of this portion of the intestine obliquely from 7 to 10 cm. from the pylorus. The accessory pancreatic duct sometimes pierces it about 2 cm. above and slightly in front of these.

The antrum, or bulbus duodenale, is a part of the superior portion of the duodenum and is directly continuous with the pylorus. In contrast to the remainder of the duodenum, its beginning portion is more freely movable and its relationship to the pancreas much looser. Schwarz has emphasized the close association of the superior portion to the stomach, both having a similar type of mesenteric fixation, similarity in behavior and appearance of the mucous membrane and similar secretory elements.

He regarded this portion of the duodenum as the "after stomach," with a smooth inner surface as differentiated from the remainder of the duodenum, which contains Kerkring folds. Åkerlund made roentgenographic studies of the stomach and duodenum in corpses, these organs being fixed in situ with formaldehyde and filled with contrast masses. Comparisons of these roentgenograms with the anatomic preparations showed that in the majority the shadow of the bulbus corresponded to the entire superior portion. Åkerlund also stated that the filling, emptying, peristalsis and tonus of the duodenal bulb are in large measure independent of the remainder of the duodenum and expressed the belief that it is an anatomic roentgenographic and physiologic entity. That portion of the duodenum from the neck of the gallbladder to the papilla of Vater is occasionally designated as postbulbar (Rutishauser).

MORBID ANATOMY

The tumor measured from 0.4 to 4 cm. in length in twenty-three cases and from 4.5 to 8 cm. in thirteen cases, and in one instance the growth involved 13 cm. of the duodenum. There was a localized growth in twenty-eight instances, thirteen of which were in the bulbar portion, eight at the superior angle and seven near the papilla of Vater. The majority of nonannular localized lesions were situated on the posterior or inferior medial wall. The suprapapillary portion of the duodenum was involved diffusely over a considerable extent in thirteen cases, the distal portion of the growth being situated near the papilla in ten, at the superior angle in two and in an indefinite location in one; the proximal margin of the growth was situated at the superior angle in four cases and in the bulbar region in nine. Neoplastic tissue was regularly found infiltrating the wall of the duodenum for varying distances, but in three cases the lesion was comparatively superficial (Herman and von Glahn and Dewis and Morse, cases 1 and 2). Opposite the primary growth a well defined tumor mass was often present on the peritoneum.

The primary growth was ulcerated in thirty instances and nonulcerated in eight, and no mention was made of this feature in three. The ulcers were round, oval or crater-like, and in the constricting lesions there were running ulcers. Their margins were thick, rolled, broad, elevated, papillated, everted or honeycombed, and either sharply defined or irregular. The base was described in only a few instances, as gray, smooth, nodular, hard or soft, and in one it was covered by greenish red material. A superficial thrombosed or ruptured blood vessel was noted in the base of the ulcer in three cases, and in two others perforation had occurred. The ulcerated lesions were generally annular and constricting but never completely obstructive in contrast to the nonulcerated type, in half of which the lesions were almost totally stenotic.

Extension or metastases were present in thirty-one cases. This is probably a conservative figure, for in several instances only the surgical specimen was examined, and in a few others autopsy was limited to the abdomen. Adhesions to the pancreas were mentioned in sixteen cases and were inflammatory, neoplastic or both. Inflammatory adhesions were associated with local ulceration and infection and probably facilitated extension of the neoplasm. Secondary deposits in the pancreas occasionally attained a large size, measuring 6 cm. in diameter. Gross appearances suggesting tumorous infiltration of the pancreas were not always confirmed histologically (Dewis and Morse, case 3, and Pacetto), whereas other tumor foci may be only microscopic in size.

Obstruction of the common bile duct was present in eleven cases, in most of which the duct was encircled by neoplastic extensions from the duodenal lesion. In Dardinski's case there were also a few small nodules in the mucous membrane of the common bile duct at the point of obstruction. Rutishauser's case 5 is sometimes cited (Willis) as an example of intracanalicular extension along the bile ducts, but from the gross description it is evidently only another example of periductal involvement. Direct infiltration of the hepatic and cystic ducts occurred in two cases. In another (Morrison and Feldman) the growth in the duodenum compressed the hepatic duct without actually invading it. Cholecystoduodenal adhesions were observed in eight cases and were dense and fibrous in all but one, in which they were fibrinous. They were proved by microscopic examination to contain neoplastic tissue only in our case 4. The falciform ligament was infiltrated with tumor tissue in three cases.

Implantation metastases occurred as discrete nodules in six cases in the mesentery, transverse colon, gastrohepatic omentum, under-surface of the diaphragm, small intestine, pelvic wall and ovary. Rutishauser's case 1 is unique in respect to the large number of implantation metastases, and the question naturally arises whether the three small duodenal lesions regarded by him as primary may not rather have been metastatic from an unidentified source. Primary carcinoma of the prostate and thyroid glands is sometimes responsible for tumor spreads of this type and extent, but these glands were not described in Rutishauser's communication.

Cancerous involvement of the regional lymph nodes was observed in sixteen cases, in four of which the nodes in the gastrohepatic omentum, around the bronchi and in the mesentery and around the aorta were also involved. Metastatic deposits were present in the liver in eighteen cases, in the lungs in one and in the fifth and eighth dorsal vertebrae in one.

Dilatation of the stomach was mentioned in twelve cases uncomplicated by gastro-enterostomy and is considerably less pronounced a feature than in carcinoma of the infrapapillary portion of the duodenum. Of seven cases in which the contents of the stomach were described, blood was found in four and bile in one. The mucous membrane of the stomach was atrophic in four cases and hypertrophic in one; the absence of free hydrochloric acid in the contents of the stomach in one of the former group was attributed to the atrophic condition of the gastric mucous membrane. The bowel distal to the primary duodenal lesion was distended and filled with blood in a few cases.

Generalized peritonitis occurred in two cases as a result of perforation of the duodenum. Small bloody effusions into the peritoneal cavity were observed in three instances, in each of which metastatic lesions were present on the serosa.

A single diverticulum of the duodenum was found in two cases, and in each of these the neoplastic growth occupied the margins of the sac (Bibby and Stewart; Morrison and Feldman).

In four cases there was obstruction of the pancreatic ducts with dilatation of the proximal ducts and atrophy of the parenchyma. In eight others there was chronic pancreatitis, the result in part of drainage of infected material from ulcerated lesions in the duodenum. Some degree of chronic pancreatitis may have existed prior to the development of cancer in three patients who gave an antecedent history of chronic cholecystitis.

Chronic cholecystitis was present in ten cases, in nine of which there were associated gallstones, gravel being present in the common bile duct in one, while in another a marble-sized calculus was removed from the ampulla of Vater.

The liver and bile passages showed the characteristic changes of biliary stasis in the cases of obstructive jaundice. There were dilatation of the large biliary ducts, proliferation of the small ducts, fibrosis of the portal radicles, degeneration and pigmentation of the parenchyma in the inner portions of the lobules, focal mid-zonal and biliary necroses and, in three cases, hepatic abscesses and cholangeitis.

HISTOLOGY

All the cases were of the glandular type of carcinoma except one, which was of the adenosquamous variety. Acinous formation was present in thirty cases and absent in one, while it was not mentioned in ten. The acini were irregular in four cases and cystic in three; in four there was a papillary arrangement. The lesion was designated as mucinous carcinoma in three cases, and in several others considerable basophilic fibrillar material was present in and between the tumor cells and in the acini. The cells grew discretely in strands, nests or clumps in sixteen cases, in only one of which acinar structures were entirely absent. The cells were essentially columnar or cylindric, although pleomorphism was occasionally marked, some cells being cuboidal, round, oval, polygonal or flat. Variation in size, shape and staining of the nuclei was also frequently noted, and of fourteen cases in which mitotic figures were observed they were numerous in nine and infrequent in five. The stroma, described in seventeen cases, was minimal in four and abundant in thirteen, the scirrhous character of the latter being an outstanding feature. Areas of hemorrhage and necrosis were often observed, and the connective tissue was regularly infiltrated with small round cells and occasionally with polymorphonuclear neutrophils and eosinophils. The inflammatory reaction was frequently intense about areas of ulceration and necrosis, and in one case there were multiple areas of suppuration. In Lageder's case the tumor varied considerably in the various sections, being almost entirely scirrhous in some and very cellular in others, forming acini occasionally with papillary projections, and in one section polymorphism was pronounced, hyperchromasia the rule and mitotic figures numerous. One section also showed a transformation into epidermoidal elements, with voluminous cells occurring singly and in groups of from ten to twenty or more to form large plaques, the centers of which showed fusion of cytoplasm and beginning keratinization.

Malignant transformation occurred at the margin of the ulcer in four cases and in the superficial and deeper portions of the mucosa in one case each, while in one subject the ulcerated surface was formed by muscle infiltrated by neoplastic cells, both edges of the ulcer presenting atypical glandular formation resembling somewhat the picture seen in chronic ulcer.

CLINICAL FEATURES

Onset.—The cases were divided on the basis of onset into three groups: acute onset, twenty-two; gradual onset, seventeen, and indefinite onset, two. This division was made irrespective of an antecedent history of symptoms referable to the upper portion of the abdomen, which was elicited in twelve of the cases in which the onset was acute and in four of the cases in which it was gradual.

In the cases in which the onset was acute there were many symptoms, chief among which were the following: vomiting (fourteen cases), epigastric pain (twelve), weakness and loss of weight (eleven), jaundice (six), anorexia (six), flatulence (five), belching (five), sense of pressure or weight in the epigastrium (four) and constipation (three). The duration of symptoms in eighteen of these cases ranged from one week to nine months, with an average of about three months. In three of the remaining four cases the onset occurred from three to six months before admission; the patients in two of these cases were not heard from after discharge from the hospital, and the patient in the other case died within two years. In the other case, despite the fact that symptoms had existed for one and a half years, the onset was acute, due apparently to biliary obstruction by infiltrating carcinomatous tissue.

The duration of symptoms in the gradual group ranged from six months to four years, with an average of sixteen months. The early symptoms were pain (eleven cases), dyspepsia, heaviness or distress (eight), loss of weight (eight), vomiting (four), weakness (five), anorexia (four) and jaundice (two). An acute exacerbation or sudden change in symptomatology occurred in ten of these. The average duration of this later acute phase was two months, the clinical manifestations being vomiting (five cases), epigastric pain (five), jaundice (two) and constipation (two).

As mentioned previously, a history of antecedent illness was elicited in sixteen cases. The condition was described as disease of the biliary tract in five, gastric or duodenal ulcer in five, tuberculosis in one and indeterminate lesions of the upper part of the abdomen in six, in two of which pancreatitis and pericholecystic adhesions were demonstrated at autopsy. Of five cases with a history of disease of the biliary tract, a large duodenal diverticulum was present in one, while in the remaining four operation or autopsy revealed calculous cholecystitis.

The five cases in which duodenal or gastric ulcer was suspected were reported by Letulle, Jefferson, Ramond, Vincent and Clément, Kettle and Archibald. No conclusive evidence of the etiologic relationship between ulcer and carcinoma was advanced by these authors. In Jefferson's case posterior gastro-enterostomy was performed for relief of indigestion, epigastric pain and vomiting, and, according to the hospital records, an ordinary nonmalignant ulcer of the duodenum was found. Postoperative convalescence was satisfactory, and the patient continued in excellent health for two and a half years, when diarrhea and abdominal pain gradually developed, with loss of weight, and death occurred a year later. At autopsy a completely annular, almost totally obstructive carcinoma of the duodenum was found. In this case it seems reasonable to question the accuracy of the original diagnosis of simple ulcer, since no statement was made as to whether it was inspected directly by opening the duodenum, or whether biopsy was performed. Since obstructive phenomena were obviated by the procedure of gastro-enterostomy in this case, it is not improbable that the lesion was malignant from the onset.

Pain, Tenderness and Rigidity.—Pain was reported in twenty-eight cases, was absent in six and was questionable in three, while in the remaining four epigastric distress, soreness, a sense of pressure in the abdomen, heartburn or pain on deep palpation over the neoplasm were the complaints. Of two patients who did not complain of pain, one was senile and the other was a morphine addict. Pain occurred early in the disease in seventeen cases and late in five, and it was likely to appear at any time of the day or night, lasting from a few minutes to several hours. It was present in the epigastrium in fifteen cases and in the lower portion of the abdomen in two and was generalized over the abdomen in one, radiating to the back in four and to the right loin and right shoulder in one each; in one case it was at first substernal and later radiated to the eleventh dorsal segment and the epigastric region. The pain was severe in six cases, intermittent or paroxysmal in nine, continuous in three and vague or variable in two. The ingestion of food preceded the onset of pain usually by from one-half to two hours in ten cases and gave symptomatic relief in two, while in three it had no effect. Abdominal tenderness was associated with pain in ten cases and was present without pain in two cases. All three patients with abdominal rigidity had pain, and one had abdominal tenderness. Pain was associated with vomiting and sour eructations in two cases, while in three others it was relieved by vomiting or belching or by the administration of alkali; in one case pain and other symptoms disappeared following cholecystectomy and choledochogastrostomy. No correlation could be established between the symptom of pain and the situation and size of the primary growth or adhesions to and neoplastic infiltrations of surrounding structures.

Vomiting.—Vomiting occurred in twenty-six cases, was absent in six and was not mentioned in nine. This symptom occurred in sixteen cases in which the onset was acute, in seven cases in which the onset was gradual at first and then became acute, in two cases in which the course was gradual throughout and in one case in which the onset was indefinite. Of the cases in which the onset was acute, vomiting was an early symptom in ten and developed later in six. Of the cases in which the onset was at first gradual and then acute, vomiting occurred with the gradual manifestations in only two and coincidentally with the acute manifestations in five. Of the cases in which the course was gradual throughout, vomiting was an early symptom in one and appeared later in another. Nausea and vomiting usually occurred together, the nausea appearing a week or so before vomiting commenced, the latter tending to become incessant terminally. Vomiting was initiated or exaggerated bv food in nine cases, while in ten no such relationship was established. The vomitus contained blood in several instances, as well as particles of food which had been ingested from one to ten days previously and which sometimes exhibited evidences of putrefaction. Biliary vomiting was present in only one case in which the bile drained into the stomach through a choledochogastrostomy opening, the operation having been performed early in the course of the disease.

Absence of vomiting was definitely stated in six instances. In the first of these the symptoms were not described in detail during an eight month interval between exploratory laparotomy and death. In another the dimensions of the primary lesion were not accurately stated. In a third the presence of a gastro-enterostomy opening obviated the effects of duodenal obstruction. In the other three cases the primary duodenal carcinoma was small, measuring, respectively, 0.6, 1.8 and 2 cm. in the greatest diameter. From this analysis it is evident that vomiting occurs regularly with the onset of intestinal obstruction but develops occasionally before there is any appreciable encroachment of the primary lesion on the lumen of the intestine. It is also possible that ulceration of the primary lesion may in some instances permit the passage of duodenal contents, and in such cases vomiting may be absent.

Jaundice.—Jaundice was present in seventeen cases, absent in fourteen and not mentioned in eight. It occurred with the acute symptoms in nine and from five to seven months after the onset in six, while in two its time of occurrence was not stated. It was due to neoplastic infiltration of the common bile duct in six cases, neoplastic obstruction of the hepatic duct in two, metastatic carcinoma of the head of the pancreas in one, pressure of the primary tumor and associated diverticulum in one and stone in the ampulla of Vater in two. In five cases the cause of jaundice was not accurately stated in the reports but was probably due to biliary obstruction. The location of the obstruction in the biliary tract depends to some extent on the segment of duodenum involved by the neoplasm; thus, in two cases in which the carcinoma originated near the pyloric orifice the hepatic ducts were obstructed, whereas neoplastic involvement of the lower end of the common bile duct was associated with tumors arising just above the papilla of Vater. Of the four cases with jaundice in which the duodenal growth was localized at the superior angle, biliary stasis resulted from neoplastic invasion of the common duct and hepatic duct (one case each), stone in the ampulla of Vater (one) and compression of the bile ducts by a combination of diverticulum and primary neoplastic lesion (one).

Jaundice was regularly associated with clay-colored stools and bilirubinuria and increased progressively in intensity unless surgical measures were instituted for its relief. In Mateer and Hartman's case the icterus index, estimated every second day for a period of two weeks, increased from 27 to 74, duodenal drainage on two occasions yielding no bile. Pain was present in eleven cases in which jaundice was present, in five there was no pain and in one this symptom was not mentioned.

Pain and jaundice occurred simultaneously in six cases, in two in association with cholelithiasis, and in five jaundice followed the appearance of pain.

Constipation and Diarrhea.—Constipation or obstipation occurred in fourteen cases and diarrhea in six cases, while in about 50 per cent the bowels were normal or there was no mention of abnormality. Constipation occurred with the onset in five cases and after the onset in three; of two cases in the former group, this symptom abated somewhat subsequently, being followed by diarrhea in one instance. Diarrhea, when it occurred, was usually persistent.

PHYSICAL EXAMINATION

A mass was palpated in the region of the primary tumor in ten cases, no evidence of a mass was detected in nineteen and there was no mention of this feature in the remainder. Although each of the following characteristics of the palpated mass was mentioned at least once, few details were available as to its size, shape, consistency, fixation, mobility, movement with respiration and continuity with liver dulness. In four cases there was associated tenderness.

It seemed of value to correlate the presence or absence of a palpable mass with the size of the local neoplasm and associated inflammatory lesions as demonstrated at autopsy. In doing this, the morbid anatomy of the condition was evaluated not so much in respect to the duodenum, pancreas, lymph nodes or serosa singly but rather in relation to the size of the lesions as a whole. For example, if the combined and associated neoplastic and inflammatory processes were extensive, the anatomic lesion was graded as large, even though the primary tumor in the duodenum was small. Of the ten cases in which a mass was palpated clinically, the anatomic lesion was graded as large in all but one. Of the cases in which a mass was not palpable or not mentioned clinically, the anatomic lesion was graded as large in sixteen cases and as small in fifteen. Local conditions may have interfered clinically with the palpation of a large anatomic lesion in seven cases, for in four there was a marked degree of rigidity or abdominal distention, in two the neoplasm was situated on the posterior wall of the duodenum and in the other there were dense local adhesions between the inferior margin of the liver and the anterior abdominal wall.

The liver or gallbladder or both were palpable in nine cases, in all of which obstructive jaundice was present. In one case the liver was enlarged and nodular and at autopsy showed metastatic nodules and biliary stasis. Dilatation of the stomach to the level of the umbilicus or symphysis pubis was noted in five cases, a succusion splash was heard in two and abdominal peristalsis was marked in three.

LABORATORY STUDIES

Analysis of the Gastric and Duodenal Contents.—Aspirated gastric contents or vomitus were examined in fourteen cases. Blood was present in eight instances and bile in one; in the latter choledochogastrostomy had been performed. Free hydrochloric acid was present in seven cases, absent in five and not mentioned in one; it was absent before and after a test meal in two, while in another it rose from 19 to 30 after this procedure. Total acidity ranged from 25 to 100 in ten cases, the average being 64. After a test meal the total acidity decreased from 87 to 45 in one case and rose from 34 to 49 in another. Duodenal drainage was carried out in only one case and yielded no bile on two attempts, the patient being jaundiced clinically; autopsy revealed obstruction of the common bile duct.

Stools.—The stools were examined in twenty-two cases, in fourteen of which blood was found either grossly or by chemical examination. The stools were acholic in nine cases, in all of which there was obstruction of the extrahepatic biliary passages. In eight additional cases of biliary obstruction, the stools contained large amounts of blood in four and were not examined in four. Typical "pancreatic" stools were found in only one case, in which the duct of Wirsung was obstructed and the duct of Santorini could not be found. In three others in which there was postmortem evidence of obstruction of the pancreatic ducts, the character of the stools was not described.

Blood Studies.—The red blood cell count or hemoglobin determination or both were reported in fourteen cases. These were normal in one case, in which, however, there was frequent vomiting, which may have produced some degree of hemoconcentration. In two cases hemoglobin estimations alone were reported and were below normal in each. In the remaining eleven cases there was marked anemia. In seven of these the color index was low, and in three it was high (1.01, 1.03 and 1.15). These findings contradict the opinion expressed by a number of authors that anemia is not a prominent feature in cases of duodenal cancer. The blood count may not be a true index of the degree of anemia, which may be masked by hemoconcentration due to dehydration incident to frequent vomiting. Loss of blood by hemorrhage occurs frequently, for blood was found in eight of fourteen specimens of gastric contents and in fourteen of twenty-two stools examined clinically; in several subjects extensive intestinal hemorrhage was demonstrated at autopsy.

Roentgenographic Examination.—The stomach and duodenum were examined roentgenographically after an opaque meal in eighteen cases, in eleven of which there was a demonstrable lesion. However, the true nature of the lesion was strongly suspected in only two cases (Mateer and Hartman, and Bastos), while in the remainder the following diagnoses were made: ulcer (three cases), duodenal *stenosis* (*two*), carcinoma of the stomach (two) and adhesions and obstacle at the pylorus (one each). A filling defect was noted in the region of the pylorus in three cases and in the second portion of the duodenum in four, in one of which there was also a constant deformity of the duodenal cap, which was interpreted as due to displacement; in the remaining four cases no filling defect was described. The case reported by Herman and von Glahn demonstrated the value of comparing the roentgenograms with the morbid anatomic specimen. In this case the roentgenograms of the gastro-intestinal tract were reported as essentially normal, and although the length of the "stalk" of barium was commented on at the time, it was interpreted as the stream passing through the pylorus. Comparison with the postmortem specimen showed that the neoplasm had formed a canal through which the gastric contents passed, and this "stalk" represented the stream of barium passing through the lumen of the duodenal growth.

There were seven cases in which no lesion was demonstrated roentgenographically. In one case aggravated vomiting interfered with the examination, and in another there was considerable retention of food. The anatomic lesions present in the remaining five cases are described briefly. In Pacetto's case there was a firm fibrous ulcerated obstruction, measuring 4 cm. in length, which involved two thirds of the circumference of the first portion of the duodenum. In Meyer and Rosenberg's case the suprapapillary segment of the duodenum was greatly narrowed by an annular papillary mass extending from just beyond the pylorus almost to the papilla of Vater. McGuire and Cornish found an infiltrating mass at the lower border of the liver and connecting with the duodenum, but the dimensions and appearance of the lesion in the mucous membrane of the duodenum were not described. In Van Tienhoven's case there was an ulcerating "brussel sprout-like" lesion on the pyloric side of the papilla of Vater, which was entirely free of neoplastic tissue. In Oschner and Wilbur's case an irregular area of ulceration, measuring 4 by 1.5 cm., was found 3 cm. below the pylorus.

It has been emphasized by others that roentgenographic studies in cases of cancer of the suprapapillary portion of the duodenum are of considerable value from a negative standpoint. Thus in patients exhibiting signs and symptoms referable to the gastro-intestinal tract, such studies may rule out the possible presence of organic lesions of the stomach, colon or gallbladder. The difficulty of visualizing carcinoma in this region can be attributed to several important factors. For one thing, the distal two thirds of the duodenum empties rapidly and is usually not entirely filled at any one time. Furthermore, as a rule it is not possible to distinguish defects in the suprapapillary segment from deformities due to ulcer. Even with obstruction of a relatively high grade associated with a large tumor, the only significant findings may be slight alteration in the mucosal patterns as outlined by remnants of the barium. Fixation and rigidity may be of some aid in excluding a diagnosis of benign tumor but are of no value in ruling out extrinsic cancers invading the duodenum from adjacent organs and structures such as the stomach, bile ducts, gallbladder, pancreas and lymph nodes. Gastric retention in the presence of a "vacuole" in the bulb may suggest tumor but does not exclude a growth at the pylorus or prolapse of the gastric mucous membrane into the duodenum.

Results in Cases in Which Operation was Performed

Year	Author	Operation	Result
1905	Gerster	Cholecystectomy	Died 22 hr. after operation
1906	Geiser		
	Case 1	Gastro-enterostomy; jejunostomy	Died 2 days after operation
1916	Jefferson	Gastro-enterostomy	Died 3½ yr. after operation
1920	McGuire and Cornish		
	Case 3	Duodenostomy	Operative recovery; discharged
1921	Van Tienhoven		
	Case 3	Cholecystogastrostomy	Operative recovery; discharged
1927	Morrison and Feldman	Exploratory	Operative recovery; died 7 mo. later
1928	Dewis and Morse		
	Case 1	8/6/26: gastro-jejunostomy; 10/21/26: resection of pylorus and first portion of duodenum	Operative recovery; discharged
	Case 2	Excision	Operative recovery; discharged
	Case 4	Choledocholithotomy	Died 6 days after operation
	Case 5	Excision	Died 4 days after operation
1930	Archibald	Exploratory	Died 21 days after operation
1931	Pacetto	Gastro-jejunostomy	Died 5 days after operation
1932	Mateer and Hartman	Exploratory	Died 9 days after operation
1932	Rutishauser		
	Case 5	Gastro-enterostomy	Died 3½ mo. after operation
1932	Cave		
	Case 8	2/11/14: appendectomy; 7/6/14: cholecysto-enterostomy; 10/20/14: gastro-enterostomy	Died 3 mo. after operation
1933	Eger		
	Case 1	12/24/31: gastro-enterostomy; 4/6/32: cholecystostomy	Died 10 mo. after operation
1934	Dardinski	Gastro-jejunostomy; cholecystostomy	Died 2 days after operation
1936	Stewart and Lieber		
	Case 1	1/2/30: cholecystectomy, choledocholithotomy and choledochostomy; 4/4/30: choledochogastrostomy; 4/14/31: gastro-enterostomy	Died 3 days after operation

DIAGNOSIS

A correct preoperative clinical diagnosis was made in only two cases, and in these on the basis of the roentgenographic picture (Mateer and Hartman and Bastos). A clinical diagnosis of carcinoma of the stomach or pylorus was made in eight cases, of duodenal ulcer in two, and of intestinal obstruction in two, while the following diagnoses were mentioned once: malignant obstruction of the common bile duct, carcinoma, disease of the gallbladder, carcinoma of the gallbladder or pancreas, acute indigestion, empyema of the gallbladder, tuberculous peritonitis, calculous cholecystitis, an inflammatory process of the duodenum and probable carcinoma of the duodenum with obstruction of the common bile duct. A correct diagnosis was made at operation in ten of eighteen cases; the other diagnoses were carcinoma of the pancreas (two cases), carcinoma of the pylorus (one), fibrous obstruction of the duodenum (one) and malignant obstruction at the ampulla of Vater (one); no diagnosis was recorded in three of the surgical cases. When gastro-enterostomy is done early and the malignant character of the lesion is not suspected, the subsequent clinical improvement may be so marked that a correct diagnosis is deferred until the late stages of the condition.

Early accurate diagnosis of carcinoma of the suprapapillary portion of the duodenum depends largely on thorough evaluation of the symptom complex which antedates the onset of intestinal obstruction. These early symptoms consist of vague mild complaints present intermittently for months, characterized by dyspepsia, intermittent attacks of pain, abdominal discomfort, loss of appetite and loss of weight. A mass is rarely palpable at this stage of the disease, and the roentgenographic studies are of little direct help. Later the basic symptoms in the majority of cases are those referable to intestinal and biliary obstruction. It is probable that the lumen of the intestine is temporarily obstructed for a few hours or so, followed by relief for several hours, days, weeks or even months before another attack occurs. As the disease progresses, the clinical manifestations of obstruction recur more frequently until finally nausea and vomiting develop in the vast majority of the patients. The relative incidence of the various clinical symptoms and signs and laboratory findings has been discussed under their respective headings.

TREATMENT

Reports of roentgen and radium therapy have been presented by Levin and Bastos. The results of surgical intervention in the patients in this series have not been encouraging. No instance of definite cure has as yet been recorded. As indicated in the table, seven patients died shortly after operation and four others within six months; two survived a little over a year and one two years. The subsequent fate of four patients who survived operation and were discharged from the hospital is not known. Technical considerations of the surgical treatment of carcinoma of the duodenum have recently been described by Pack and Scharnagel and Whipple, Parsons and Mullins. The difficulties that are frequently encountered may be illustrated by the fact that in the majority of cases analyzed, the process was extensive, ulcerating and constricting and frequently involved adjacent structures. In the present series, the regional lymph nodes were invaded by metastases in sixteen cases and the bile ducts in twelve, and there were either neoplastic or inflammatory adhesions to the pancreas in sixteen cases and to the gallbladder in eight. Obviously the measures to be employed in any individual case must depend on the condition of the patient, the character and extent of the lesion and the presence and degree of intestinal or biliary obstruction.

SUMMARY AND CONCLUSIONS

This study of carcinoma of the suprapapillary portion of the duodenum represents a clinical and pathologic correlation based on six new cases and thirty-five cases reported in the literature; references to sixty-eight additional cases reported as examples of this condition are listed.

One case was found in 3,526 autopsies (0.028 per cent) and four cases in 20,176 autopsies (0.019 per cent).

The average age was 55.75 years, twenty-four of the patients being men and fifteen women.

The onset was acute in 53.6 per cent of cases and gradual in 41.4 per cent, an antecedent history of symptoms referable to the upper portion of the abdomen being elicited in approximately half of the cases in which the onset was acute and in several in which it was gradual. The symptoms occurring most frequently in the cases in which the onset was acute were vomiting, epigastric pain, weakness, loss of weight and jaundice, and the average duration of life was three and a half months. The early symptoms occurring most frequently in the cases in which the onset was gradual were abdominal pain, dyspepsia, loss of weight, vomiting and jaundice, and the average length of life after the onset was sixteen months. A marked change in symptomatology occurred in 62 per cent of the cases in which the onset was gradual, symptoms occurring which resembled those in the group in which the onset was acute. A mass was palpated clinically in the region of the primary tumor in approximately 24 per cent of the cases. The gastric or duodenal contents contained blood in eight of thirteen cases, free hydrochloric acid in seven, and bile in only one in which cholecystogastrostomy had been performed. The stools contained blood in thirteen of twenty-one cases, and nine were acholic; typical "pancreatic" stools were found in one case in which the duct of Wirsung was obstructed. A marked grade of anemia was present in ten cases, the color index being low in seven and high in three. Roentgenographic studies are of little direct value in making a positive diagnosis of carcinoma of the suprapapillary portion of the duodenum. In a few cases evidence of an ulcerated lesion in the duodenum or of obstruction of the gastro-intestinal tract was suggested but, on the other hand, extensive constricting lesions were frequently not demonstrated. Irrespective of the anatomic point of obstruction, the findings are frequently interpreted as pyloric obstruction. This method of examination is of greatest value in ruling out lesions of the stomach, colon or gallbladder.

A correct preoperative clinical diagnosis of carcinoma of the suprapapillary portion of the duodenum was made only twice. A correct surgical diagnosis was made in nine of seventeen cases, biopsy being of especial value in this connection. No instance of cure has been recorded, although follow-up studies were incomplete in a few cases.

The growth averaged 2.5 cm. in length in 56.1 per cent of cases and varied from 4.5 to 8 cm. in length in 31.7 per cent. It was localized in 68.3 per cent of cases, and in one half of these to the bulbar region. Ulceration occurred in about 73 per cent of cases, about half of these being annular or constricting lesions. Extension or metastasis occurred in 75.6 per cent of cases, to the liver, lymph nodes, pancreas, biliary passages, peritoneum, lungs and bone. All the growths were adenocarcinoma but one, which was an adenosquamous cell carcinoma.

No definite evidence has been advanced to support the hypothesis that simple ulcer of the duodenum is a precancerous lesion.

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CONCEALED HEMORRHAGE INTO TISSUES AND ITS RELATION TO TRAUMATIC SHOCK

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Evident hemorrhage, such as that from a cut vessel, with external bleeding has long been recognized as a factor of importance in traumatic shock. In certain instances during a surgical operation, when the blood is distributed on a large number of sponges, sheets and towels, the full extent of the hemorrhage is sometimes not realized. But at least it is recognized as being a factor of importance and is treated by methods intended to restore the loss of circulating fluid.

On the other hand, there are many instances in which the hemorrhage is hidden and not recognized. The shocklike symptoms that develop in patients so affected are attributed to the action of a variety of ill defined agents, such as the toxic action of traumatized tissue, anociassociation, etc. The exact relationship between the cause and the condition being indirect and uncertain, the treatment is equally indefinite. It is with the intention of showing that some of these patients suffer from hidden hemorrhage sufficient to account for their symptoms that this paper is written. Such hidden hemorrhage may be either (1) into a body cavity, such as the pleural or peritoneal cavity, or into a hollow organ, or (2) into the tissues. The first type is generally recognized as being of importance and is overlooked usually because of inability or failure to make an adequate physical examination. The second type of hidden hemorrhage is allowed to pass unrecognized in most clinical cases because its importance is not generally realized.

In experimental work on traumatic shock it was only recently that the full importance of hidden hemorrhage and extravasation of plasma into the tissues was recognized. Bayliss and Cannon[1] in 1919 performed experiments on cats wherein one hindleg was severely traumatized and the other left as a control. After death of the animal the two legs were amputated and the weights compared. There was not enough difference in weight to attribute death to hemorrhage into the tissues. Later observers, however, including Phemister,[2] Blalock[3] and Parsons and

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[1] Bayliss and Cannon, cited by Parsons and Phemister.[4]

[2] Phemister, D. B.: The Vascular Properties of Traumatized and Laked Bloods and of Blood from Traumatized Limbs, Ann. Surg. **87**:806-810 (June) 1928.

[3] Blalock, A.: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:959-996 (June) 1930.

Phemister,[4] repeated the experiments of Bayliss and Cannon but amputated the traumatized limb at a higher level, so as to include the loose tissue spaces of the inguinal region into which much of the extravasated blood and plasma had diffused. The difference in weight between the two hindlimbs was found by Parsons and Phemister sometimes to be as much as 60 per cent of the total volume of blood.

Division of the caudal portion of the animal into two hindquarters and variants of this method were used by other authors to demonstrate the importance of local loss of blood and plasma in other types of shock. Loss of nearly whole blood occurs in shock due to trauma to an extremity, in portal obstruction (Elman and Cole[5]) and in intestinal strangulation (Scott and Wangensteen[6]). Loss of plasma-like fluid occurs in burns (Blalock,[7] Underhill[8] and Harkins[9]), in freezing

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[4] Parsons, Eloise, and Phemister, D. B.: Hemorrhage and "Shock" in Traumatized Limbs, Surg., Gynec. & Obst. **51**:196-207 (Aug.) 1930.

[5] Elman, Robert, and Cole, Warren H.: Hemorrhage and Shock as Causes of Death Following Acute Portal Obstruction, Arch. Surg. **28**:1166-1175 (June) 1934.

[6] Scott, H. G., and Wangensteen, O. H.: Blood Pressure Changes Correlated with Time, Length, and Type of Intestinal Strangulation in Dogs, Proc. Soc. Exper. Biol. & Med. **29**:428-431 (Jan.) 1932; Blood Losses in Experimental Intestinal Strangulations and Their Relationship to Degree of Shock and Death, ibid. **29**:748-751 (March) 1932.

[7] Blalock, Alfred: Experimental Shock: VIII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, Arch. Surg. **22**:610-616 (April) 1931.

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[9] Harkins, H. N.: Shift of Body Fluids in Severe Burns, Proc. Soc. Exper. Biol. & Med. **31**:994-995 (May) 1934; Experimental Burns: I. The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns, Arch. Surg. **31**:71-85 (July) 1935; The Bleeding Volume in Severe Burns, Ann. Surg. **102**: 444-454 (Sept.) 1935.

(Harkins, Harmon and Hudson[10]), in intestinal trauma (Johnson and Blalock,[11] and Roome, Keith and Phemister[12]) and in peritoneal irrigation by hypertonic solutions (Domenech-Alsina and co-workers[13]).

REPORT OF CASES

In all cases of wounds and trauma there is some swelling. Hemorrhage occurs in some and only edema in others. In some instances this swelling may be marked and may be a vital factor. The following cases are intended to illustrate the importance of quantitative studies of the amount of swelling after trauma. The fluid present in these swellings contains a higher percentage of proteins than ordinary edema fluid, and hence its loss may lead to circulatory disturbance.

CASE 1.—Mrs. C. O'M., aged 46, had been in the hospital for three days because of a neurosis, when on March 9, 1935, at some time between 3:10 and 4 a. m., when found, she jumped out of a fourth story window, landing on a wood porch floor, a distance of 39 feet. The outdoor temperature was 27 F. at the time, and she was clad in only a thin nightgown. She was found unconscious, with a small amount of bleeding due to a laceration of the scalp. Her pulse was unobtainable, she was cyanotic and moaning and the blood pressure was not obtained for an hour and a half, when it was 60 systolic and 35 diastolic. She was given 1,800 cc. of saline solution intravenously followed by 500 cc. of blood. By 8 a. m. she was conscious, and the blood pressure had risen to 84 systolic and 40 diastolic, as shown in figure 1, but by noon it had fallen to 46 systolic, and there was a moderate cold perspiration over the upper half of the body. The red cell counts are shown in figure 1. Just before a second transfusion of 500 cc. of blood was given at 2 p. m. the count was 3,800,000. The pulse rate for two days before the accident averaged 120 (basal metabolic rate, plus 11). It ranged from 140 to 160 the first five days after the accident, and then it came down gradually to 110. The laceration of the scalp was sutured soon after the patient was discovered, and two days later roentgenographic studies revealed fractures of both innominate bones, the right ninth rib, the left radius, the right greater trochanter of the femur and the left clavicle. There were extensive ecchymoses and swellings of the right side of the chest, the right side of the abdomen and the right arm and leg. Measurements of the right side of the body were compared with those of the left side and are shown in table 1. The maximum amount of swelling was about 1,550 cc. It is to be remembered that the left side of the body may have swelled in certain places, and there may have been some hemorrhage into the thoracic and abdominal cavities not determinable by physical examination. Furthermore, as the interval between the time the patient was last seen in her room and that when she was found on the porch floor amounted to fifty minutes, the effects of exposure to cold have to be considered. The first comparative

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[10] Harkins, H. N.: Shock Due to Freezing: I. Shift of Body Fluids and Associated Blood Concentration Changes, Proc. Soc. Exper. Biol. & Med. **32**:432-434, 1934. Harkins, H. N., and Hudson, J. E.: Shock Due to Freezing: II. Composition of Edema Fluid, ibid. **32**:434-435, 1934. Harkins, H. N., and Harmon, P. H.: Experimental Freezing: Bleeding Volume, General and Local Temperature Changes, ibid. **33**:1142-1143, 1935.

[11] Johnson, G. S., and Blalock, Alfred: Experimental Shock: XII. A Study of the Effects of Hemorrhage, of Trauma to Muscles, of Trauma to the Intestines and of Histamine on the Cardiac Output and on Blood Pressure of Dogs, Arch. Surg. **23**:855-863 (Nov.) 1931.

[12] Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, Surg., Gynec. & Obst. **56**:161-168 (Feb.) 1933.

[13] Domenech-Alsina, F.; Benaiges, B., and Arqué, P.: Etude du choc provoqué par l'irrigation péritonéale hypertonique, Compt. rend. Soc. de biol. **114**: 104-105 (Feb. 12) 1933.

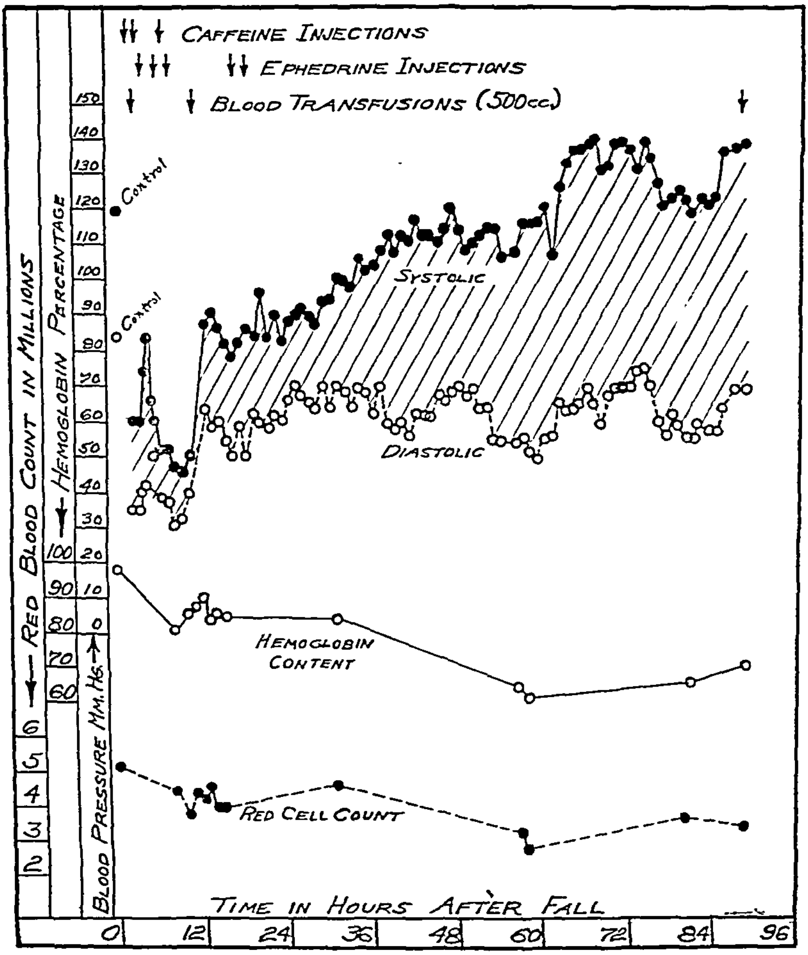

Fig. 1 (case 1).—Chart showing the course of blood pressure and blood concentration after traumatic shock associated with multiple fractures and local swelling. Injections of epinephrine hydrochloride administered subcutaneously and 1,800 cc. of physiologic solution of sodium chloride administered intravenously were given at the same time as the first injection of caffeine sodiobenzoate. The prolonged lowering of blood pressure over a period of forty-eight hours with recovery is of interest.

measurements were recorded twelve hours after the accident. Other readings taken almost daily during the next two weeks showed no further swelling. Nine days after the accident the asymmetry began to disappear; in twelve days it had almost disappeared, and two weeks after the injury measurements on the two sides were about equal. The measurements were taken at different points, and the volume was calculated for each segment as that of a frustum of a cone. A rough estimate of volume is thus derived from the well known formula:

$$V = 1/3\,\pi\,h\,(r_1^2 + r_2^2 + r_1 r_2)$$

In this patient the steady fall in the red cell count despite the absence of continued external hemorrhage and of known hemorrhage into the visceral or body cavities is of interest. Continued hemorrhage into the injured tissue spaces may have been a factor. Restoration of the blood volume by an inflow of fluid from the noninjured tissues in remote parts of the body is another possible cause.

Table 1.—*Measurements of Arms, Leg and Body in Case 1* *

	Right Side		Left Side	
Point of Measurement	Circumference, Cm.	Volume, Cc.	Circumference, Cm.	Volume, Cc.
5 cm. above elbow	29.0	308	28.5	292
Elbow	26.5	270	25.5	244
5 cm. below elbow	25.5		24.0	
22 cm. above patella	59.5	2,390	55.5	2,070
12 cm. above patella	49.5	3,060	46.0	2,730
12 cm. below patella	30.5		29.5	
Semicircumference of abdomen	42.0	5,605	39.0	4,845
Total		11,633		10,181
Excess		1,552		

* The excess volume of the right arm is inappreciable, while that of the right leg and the right side of the body is considerable. *It is not known, however, that the opposite limbs or* portion of the abdomen were of normal size. The volume of the halves of the abdomen is calculated as that of a half of a cylinder with the semicircumference given, and a length of 20 cm., that is, approximately the extent of the ecchymotic region on the right side. The excess of 1,550 cc., if composed of blood or plasma, would be a factor of importance in the production of traumatic shock.

Case 2.—Mrs. C. L., aged 42, received fractures of the left femur, left tibia and both bones of the left forearm just before admission to the hospital. The volume of about two thirds of the left thigh was 8,900 cc. by measurement and of a corresponding portion of the right thigh 7,100 cc., representing a swelling of 1,800 cc. However, since there was 1.5 cm. shortening of the thigh due to fracture, using the average circumference of the thigh as 50 cm., the corrected swelling was 300 cc. less, or about 1,500 cc. This did not include the swelling of the arm or tibial region. A good portion of this swelling was present within a few hours after the injury; it was somewhat more marked in three days and had absorbed to some extent in ten days.

The blood pressure was 94 systolic and 68 diastolic two hours after the patient's admission, and she was given a transfusion of 650 cc. of blood immediately and a similar transfusion four days later. The red cell count was 3,900,000, the hemoglobin content 70 per cent (Sahli) and the hematocrit reading 34 on the day of admission (after a blood transfusion). The red cell count two days later was 2,600,000 and gradually rose thereafter.

CASE 3.—Mrs. J. L., aged 51, entered the hospital an hour and a half after a severe automobile accident with fractures of the shaft of the left femur, the right tibia and the fibula in two places (the upper and the lower third), both bones of the right forearm, the right innominate bone, a 3 inch incised wound of the scalp and a jagged 5 inch incised wound of the wall of the lower part of the abdomen. The amount of hemorrhage from the external wounds had been relatively small, while there was great swelling around the sites of the fractures. These swellings were not measured. There were no specific signs of fat embolism. The blood pressure on admission was 60 systolic and 40 diastolic, and after the administration of 1,500 cc. of Ringer's solution intravenously, it rose to 114 systolic and 74 diastolic five hours after the accident. It remained around 120 systolic until forty-eight hours after the accident, when it fell to 98 diastolic and 60 systolic. Transfusion of 500 cc. of blood restored it to normal, where it remained. The hemoglobin content and the red cell count fell steadily over the forty-eight hour period before the blood transfusion, despite the fact that all external hemorrhage was controlled, and there was no demonstrable hemorrhage into the body cavities or viscera.

TABLE 2.—*Changes in the Blood Concentration in Case 3*

Time	Hemoglobin Content	Red Cell Count, Millions
On admission	93	5.2
14 hours later	85	4.3
18 hours later	60	3.4
36 hours later	..	3.7
48 hours later	55	2.9
50 hours later	Blood transfusion, 500 cc.	
60 hours later	60	3.2
64 hours later	58	2.9
84 hours later	60	3.5
108 hours later	60	3.9
160 hours later	68	4.2

Continued hemorrhage into the tissues at the sites of injury on the one hand and secondary effects of restoration of blood volume by inflow of tissue fluids at places remote from the injuries on the other hand are possible explanations of this continued dilution of blood just as in case 1. The blood changes are shown in table 2. Technical errors in determination of the hemoglobin percentage and red cell count undoubtedly account for some of the minor variations.

CASE 4.—Mrs. C. S., aged 58, was admitted to the hospital with multiple fractures, a blood pressure of 50 systolic and 40 diastolic and the typical picture of traumatic shock following an automobile accident.[14] Despite blood transfusion and the administration of other fluid intravenously, she died eight hours after admission. Necropsy revealed a loss of about 1,200 cc. of blood at the site of numerous fractures and from traumatic rupture of the aorta. In this case the concealed hemorrhage was partly into the tissues and partly into the pleural cavity and the mediastinum.

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[14] This case has previously been reported in full by Wilson, H., and Roome, N. W.: Am. J. Surg. **22**:333-334 (Nov.) 1933.

CASE 5.—Mr. J. P., aged 34, underwent a disarticulation of the hip for chronic osteomyelitis of the femur and suppurative gonitis on June 5, 1935, with a blood pressure reaction (fall to 96 systolic and 78 diastolic an hour after operation with prompt recovery). Twelve days later the patient became much worse, and it was found that he had bled about 1,000 cc. into the amputation stump. The blood pressure had again fallen to 98 systolic and 52 diastolic. He was given two blood transfusions totaling 1,000 cc. that day, with a rise in pressure to 105 systolic and 74 diastolic and eventual recovery. Marked edema involving especially the face disappeared soon after the transfusions and may have been due to a low level of plasma protein.

CASE 6.—Mrs. C. M., aged 30, caught her right hand and the lower half of the forearm under a folding sofa. Because she was alone in the house, it was five hours before she could be released. On admission to the hospital soon after, the hand appeared as shown in figure 2 with huge blisters. The blister fluid contained amounts of nonprotein nitrogen and sodium chloride similar to the composition of blood plasma, and it clotted spontaneously. The volume of the hand and forearm, as measured by a plethysmograph twelve hours after admission, was 600 cc. greater than the volume of the left hand and forearm. The red cell count at that time was 7,100,000, and the hemoglobin content was 95. The next day the red cell count was 6,600,000, and five days after admission it was 4,700,000. The blood pressure remained normal throughout. It seems unlikely that this amount of swelling could have produced all the blood concentration.

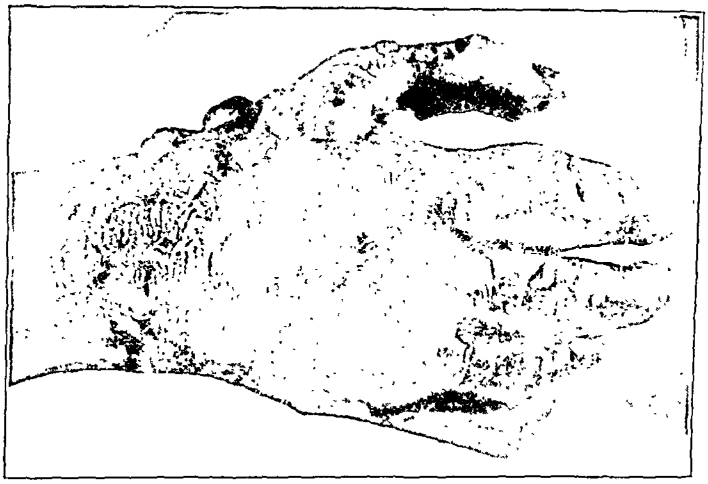

Fig. 2 (case 6).—Extreme swelling of hand of patient C. M. taken eighteen hours after the accident.

CASES 7-10.—These four cases represent instances of minor injuries in which quantitative measurement of the resultant swelling was made. In none of them was the trauma sufficient to cause shock, a fall in blood pressure or changes in the concentration of blood. Jack F., aged 4 years, had an increase in the size of the left thigh (measurement) of 200 cc. six hours after receiving a fracture of the left femur. Mrs. J. M. and Mrs. F. W. each ran her left arm through a wringer almost to the elbow. The first patient had a swelling of 260 cc. (measurement) and 300 cc. (plethysmograph) and the second patient of 250 cc. (measurement). The readings in both instances were taken twelve hours after the injury. Two hours after a fracture of both bones of the right leg, Mrs. McM. had a swelling of 300 cc. (measurement) of the affected leg.

COMMENT

In some of the cases reported here concealed hemorrhage into tissues followed injury of such a slight degree that the loss of blood was not great enough to lead to shock. In only one case (case 4) did death result, and in this instance there was in addition bleeding into a body cavity and external bleeding. However, the lesson learned from the minor injuries of the group, namely, that there may be considerable loss of blood into the tissues which is not visible on casual examination, can be applied to more serious injuries. If a simple crushing of the hand and forearm can produce an increase in the local volume of several hundred cubic centimeters in a few hours, more extensive body injuries could easily produce a change of several times that much.

The measurements of circumferences of the limbs and body and subsequent calculation of the difference in volume on the two sides from the volumes of a series of frusta of cones is not expected to be an exact quantitative method. However, check measurements usually agreed quite well, and the volumes calculated were in all instances greater on the injured side. In one case a check reading was made by the plethysmographic method which agreed well with the calculated volume difference. In another instance only the plethysmographic reading was taken.

In most instances the swelling appeared rapidly in the first few hours after injury. After reaching a maximum, it took several days to subside. The relative abounts of extravasated blood and plasma constituting the swelling was variable with the injury, but as no incisions into the swollen areas were made or analyses performed, the exact proportions were uncertain. Local discoloration and lack of marked blood concentration would indicate that in those cases at least a good share of the swelling was due to a loss of whole blood.

This proportionate loss of whole blood and plasma in certain traumatic forms of secondary shock has led to some confusion in the literature. Coonse, Foisie, Robertson and Aufranc[15] stated that traumatic shock is accompanied by blood concentration and hemorrhagic shock by anemia. Moon[16] cited the same differentiating point between the two types of shock. It is probable that the time element alone is one of the chief factors differentiating the two types. In acute hemorrhage the loss of blood is sudden in many instances, and at death what Moon calls a "dry necropsy" is found, the tissues being anemic. With a slow leak of of blood into the tissues, the blood pressure is maintained at a low level for a prolonged period of time (as in case 1). This prolonged lowering of the blood pressure alone will give rise to increased permeability of capillaries and to certain organic changes typical of Moon's "wet necropsy" that he says accompanies shock. Even Coonse and his collaborators[15] admitted that slow hemorrhage simulates traumatic shock. In many types of shock, furthermore, especially after burns or experimental intestinal manipulation, the loss of fluid is almost entirely blood plasma, and naturally hemoconcentration results. In other types of shock, such as after physical trauma to an extremity, both whole blood and plasma may be lost, and at the other end of the scale stands simple hemorrhage in which only whole blood is lost. Consider for the minute a hypothetic closed vascular system containing 5 liters of blood and with a hematocrit reading of 50 per cent: 1. If 2 liters of plasma is lost the relation will be 2,500 cc. cells and 500 cc. of plasma, and the hematocrit reading will rise to 83; later, if tissue fluids restore this loss of fluid, the hematocrit reading will again drop to 50. 2. If 1 liter of whole blood and 1 liter of plasma are lost, the relation will be 2,000 cc. cells and 1,000 cc. of plasma, and the hematocrit reading will be 67. With varying proportions of loss of whole blood and plasma, the hematocrit reading will approach normal. In actual practice, it may be below normal, and a relative anemia will result due to inflow of tissue fluids. 3. Finally, if whole blood is lost, there is no change in the hematocrit reading in a hypothetic closed system, but the accompanying inflow of tissue fluids will theoretically always produce anemia. Elman, Weiner and Cole[17] have shown experimentally that with local anesthesia hemorrhage produces anemia but that with amytal anesthesia there may even be concentration of the blood after hemorrhage. Blalock[3] concluded his discussion of this aspect of the question by saying that "there may be two types of hemorrhage, that outside the body . . . and that into the tissues."

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[15] Coonse, G. K.; Foisie, P. S.; Robertson, H. F., and Aufranc, O. E.: Traumatic and Hemorrhagic Shock: Experimental and Clinical Study, New England J. Med. **212**:647-663 (April 11) 1935.

[16] Moon, V. H.: The Shock Syndrome in Medicine and Surgery, Ann. Int. Med. **8**:1633-1648 (June) 1935.

Concerning Crile's[18] report of slight change or leukopenia in shock and leukocytosis in hemorrhage, in several of the cases presented in this paper marked leukocytosis developed after injury; for example, case 1, 33,000; case 2, 19,000; case 3, 28,000, and case 4, 28,000.

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[17] Elman, R.; Weiner, D. O., and Cole, W. H.: Effects of a General Anesthetic (Sodium Amytal) on the Erythrocyte Count Following Hemorrhage, Proc. Soc. Exper. Biol. & Med. **32**:793-796, 1935.

[18] Crile, G. W., cited by Orr, T. G.: Hemorrhage and Traumatic Shock, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1935, vol. 1, chap. 9, p. 2.

SUMMARY AND CONCLUSIONS

External hemorrhage has long been recognized as producing secondary surgical shock; concealed hemorrhage into the body cavities and hollow organs has been recognized but is often not diagnosed, while concealed hemorrhage into tissue spaces has not been universally considered as an important clinical cause of secondary shock.

Cases of concealed hemorrhage and extravasation of plasma into tissue spaces are presented. The resultant swelling is usually greater when measured quantitatively than casual physical examination would have led one to believe.

The extensive concealed hemorrhage and plasma extravasation in clinical cases substantiates the experimental observations of others that such local loss of fluid from the circulating blood stream is a factor of importance in the production of secondary surgical or traumatic shock.

IODINE CONTENT OF BLOOD IN CHOLECYSTIC DISEASE

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CINCINNATI

That normal human blood contains iodine is a matter of rather recent observation, although its presence has been suspected for many years. One of the earliest treatments for goiter was with burnt sponge, and when early in the nineteenth century it was demonstrated that sponges are rich in iodine, the employment of this drug in the therapy of goiter came about inevitably. It was in 1820 that the Swiss physician, Coindet,[1] made this clinical application. From that day to this, iodine has been the standard pharmaceutic weapon against all forms of depletion of the thyroid gland.

Yet three quarters of a century elapsed before it was discovered that the thyroid gland is itself an iodine factory. The iodine content of the normal thyroid gland was demonstrated by Baumann[2] in 1895, and this discovery led chemists and biologists to endeavor to find out if iodine existed in other body tissues, though for many years thereafter the thyroid gland and its diseases formed the center of interest. In the United States public health workers and even agricultural chemists became intensely interested in the question of iodine deficiency and the normal distribution of iodine in living tissues. Working with domestic animals, David Marine and his colleagues determined the iodine content of the thyroid glands of different species, confirming Baumann's earlier assertion that the pathologic thyroid gland always has a low iodine content. Other investigators, among whom may be mentioned Cameron, Forbes, Fenger and McClendon, made many estimations of the amount of iodine contained in such materials as food and drinking water.[3]

There remained, however, the constant difficulty of making accurate estimations, because no method had been developed sufficiently delicate

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[1] Coindet, J. F.: Découverte d'une nouveau remède contre le goître, Ann. de chim. et phys. **15**:49, 1820.

[2] Baumann, E.: Ueber das normale Vorkommen von Jod im Thierkörper, Ztschr. f. physiol. Chem. **21**:319, 1895.

[3] Orr, J. B., and Leitch, Isabella: Iodine in Nutrition, Medical Research Council, Special Report Series, no. 123, London, His Majesty's Stationery Office, 1929.

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to determine the minute quantities of iodine which are normal to most plant and animal cellular structures. This was especially true of the iodine content of blood.

DETERMINATION OF THE IODINE CONTENT OF BLOOD

When in 1922 the Swiss Goiter Commission, recognizing this need, requested the government bureau of hygiene to attempt the production of a better method, von Fellenberg,[4] of the bureau's personnel, was set to work on the problem. He succeeded in perfecting "a true micromethod for the determination of iodine," the lower limits of which were about one ten thousandth of a milligram (0.0001 mg.).

Among von Fellenberg's associates at Bern, where the experiments were conducted, was Sturm,[5] a Bavarian. After learning von Fellenberg's method, he returned to Veil's clinic at Munich, where he made numerous studies not only on the blood of patients with goiter (in whom he was primarily interested) but likewise on the blood of normal persons and of persons ill with diseases other than those involving the thyroid gland. Another student of von Fellenberg, Lunde,[6] of Oslo, Norway, further developed the master's method and in his own country studied the iodine content of the blood in normal and in thyrotoxic persons. Sturm's study was really the first noteworthy contribution on the subject of iodine values in human blood. Kendall and Richardson,[7] whom Orr and Leitch[3] credit with having presented "the first modern figure for blood iodine," had employed ox blood for most of their determinations, although a few samples of human blood had been tested prior to 1920.

The work was soon greatly extended, and determinations were made of the iodine content of the blood in many other diseases besides those of the thyroid gland. Factors influencing the results, the existence of which had been previously ignored, such as geographic location and season of the year, were now taken into consideration, and the results were judged accordingly. Thus Curtis and his collaborators[8] found:

> The average normal iodine content of human blood in Chicago is about 12γ per hundred cubic centimeters. This level falls during the winter months. It is

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[4] von Fellenberg, T.: Das Vorkommen der Kreislauf und der Stoffwechsel des Jods, Ergebn. d. Physiol. **25**:176, 1926.

[5] Veil, W. H., and Sturm, A.: Beiträge zur Kenntnis des Jodstoffwechsels, Deutsches Arch. f. klin. Med. **147**:166, 1925.

[6] Lunde, G.; Closs, K., and Pedersen, O. C.: Untersuchungen über den Blutjodspiegel bei der primären Thyreotoxikose, Biochem. Ztschr. **206**:261, 1925.

[7] Kendall, E. C., and Richardson, F. S.: Determination of Iodine in Blood and in Animal Tissues, J. Biol. Chem. **43**:161, 1920.

[8] Curtis, G. M.; Davis, C. B., and Phillips, F. J.: Significance of Iodine Content of Human Blood, J. A. M. A. **101**:901 (Sept. 16) 1933.

elevated during early menstruation and pregnancy. It is higher if the person is taking iodized salt regularly. In fact, many observations show that it is elevated by *any form of iodine medication* that has thus far been studied. Owing to the minute amount of iodine normally present within the blood, a special term of designation has been widely adopted. This, a gamma (γ) or microgram, is 0.001 mg. Thus, 100 cc. of human blood normally contains 0.012 mg. of iodine. The total iodine contained in the entire human blood stream is consequently less than 1 mg.

These same investigators, whose work was done at the Billings Hospital, Chicago, made observations on patients in that institution suffering from diseases other than those of the thyroid gland and also on normal, healthy members of the hospital staff. "The majority of hospital patients present a normal blood iodine," they wrote. "Among the diseases investigated were tuberculosis, chronic osteomyelitis, fractures, and Hodgkin's disease. The blood iodine is normal in patients with cancer. There are, however, two striking exceptions. In acute severe infections, as in septicemia, the blood iodine is elevated. It is likewise elevated in lymphatic leukemia." They concluded that the level of the iodine in the blood is controlled by the activity of the thyroid gland, and in disease of the gland, at least, the significance of the iodine content "is similar to that of the blood sugar in diabetes mellitus, and to that of blood calcium in parathyroid disease."

Yet as late as 1931, Orr,[9] who had spent a considerable time in the investigation of all methods then extant, remarked rather sadly:

> It has been made clear that the present methods in use for the estimation of iodine in very minute quantities and in the presence of organic materials are so unsatisfactory as to impede further progress in research. There is need for a standard method of estimation, suitable for use by all workers alike, that will give results closely approximating to accuracy, or results in which the standard error is constant and known.

Notwithstanding these difficulties, the importance of estimating the iodine content of the blood was more and more impressed on those members of the medical profession who had to deal with diseases of the thyroid gland. The need was particularly felt in the so-called "goiter belt" in the Eastern Central portion of the country. After 1923, when von Fellenberg's method—a great improvement on any previously tried—was introduced, more progress became possible. Other ways of estimating small iodine contents were put forward by Leitch and Henderson [10] and by McClendon.[11]

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9. Orr, J. B.: Iodine Supply and the Incidence of Endemic Goitre, Medical Research Council, Special Report Series, no. 154, London, His Majesty's Stationery Office, 1931.

10. Leitch, I., and Henderson, J. M.: Estimation of Iodine in Foodstuffs and Body Fluids, Biochem. J. **20:**1003, 1926.

11. McClendon, J. F.: The Determination of Traces of Iodine, J. Am. Chem. Soc. **50:**1093, 1928.

Late in 1932 Davis and Curtis[12] made use of the fact discovered by Winkler in 1916—that an iodide may be readily oxidized to an iodate. Using bromine for this oxidation, they were able to make quantitative determinations on the iodine content of the blood far more exact than any previously obtained. But as they admitted, the method "is by no means an easy one," requiring "experience and practice to obtain satisfactory results." The estimation of the iodine content of blood remains, therefore, a procedure which is not carried out as often as it might be for the good of the individual patient as well as for the orderly progress of an interesting and clinically valuable branch of medical science.

IODINE CONTENT OF BLOOD IN DISEASES OF THE GALLBLADDER

With the establishment of relatively simple and accurate means of determining the iodine content of blood, therapeutists were able to make practical clinical use of this valuable addition to their diagnostic equipment. Confined almost exclusively at first to disturbances of the thyroid gland, the value of determinations of the iodine content of blood in other disease conditions was soon demonstrated. For the past year and a half my associates and I have been making routine studies of the iodine content at the DeCourcy Clinic. Employed originally only in connection with goiter work, in endeavoring to arrive at a normal standard for the geographic area within a hundred miles of Cincinnati, we made more than two hundred determinations on the blood of patients suffering from other diseases as well.

In the course of these routine tests we found that the iodine content of the blood is markedly increased in cases of cholecystic disease of long standing and in cases of hepatic deficiency. We later found that in cases of acute cholecystitis there is always a high iodine content. After we had determined the normal to be from 3 to 6 micrograms per hundred cubic centimeters of blood, the following figures were obtained as an average in cases of disturbances of the liver and gallbladder:

Chronic cholecystitis with stones (20 cases)	16.6 micrograms
Hydrops of the gallbladder (4 cases)	13.6 micrograms
Carcinoma of the liver (3 cases)	650.00 micrograms
Chronic cholecystitis (stone in the common duct) (5 cases)	2,090.00 micrograms

In cases of chronic cholelithiasis the figure before the administration of dextrose was 110 micrograms. After the administration of 1,500 cc. of 5 per cent solution of dextrose the figure fell to 86.7 micrograms. All determinations were made in duplicate and are accurate within 0.2 microgram.

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[12] Davis, C. B., and Curtis, G. M.: Blood Iodine Studies: Quantitative Determination of Iodine Content of Blood, J. Lab. & Clin. Med. **18**:24, 1932.

A study of these results leads inevitably to the conclusion that the liver plays an important rôle in the metabolism of iodine. In practically all our cases of cholecystic disease of long standing as well as in the acute fulminating type the iodine content of the blood was abnormally high.

ALIMENTARY VARIATION IN IODINE CONTENT OF BLOOD

This aspect of the study of the iodine content does not seem to have received much attention from investigators. In 1933 Elmer and Luczynski[13] presented to the Biological Society of Lwów, Poland, a short note on the excretion of iodine in the bile in the fasting subject and within a short time after meals.

According to Elmer and Luczynski, certain authors (Y. Maruno) have maintained recently that in rabbits there is no physiologic incorporation of iodine in the bile. Nevertheless, many other investigators have found that physiologic iodine is present in rabbits' bile. But as the amounts found by these different workers vary greatly, it is evident that its presence in the bile must be very inconstant, ranging between wide limits, with the possibility of high values being reached under certain conditions. By contrast, in the blood there is always a relatively fixed amount of iodine, the highest figures never surpassing 20 micrograms per hundred cubic centimeters of blood. In the bile of rabbits have been found values varying from 15 to 62 micrograms per hundred cubic centimeters of blood (Maurer and Ducrue); in the bile of cattle, from 3.4 to 32.5 micrograms (Pfeifer), and in the bile of dogs, from 13 to 113 micrograms (Schittenheim and Eisler). The reason for such wide variations should be ascertained. It is noteworthy that not one of these investigators has mentioned whether the estimations were taken before or after meals.

With a view to establishing the normal ratio of the iodine in the bile to the other constituents of this body fluid for a twenty-four hour secretion period, the technic previously described was used in experiments on twelve rabbits. Bile was collected from nine rabbits during the fasting period (at least from twelve to fifteen hours after the last meal) and from three other rabbits immediately after eating (the ration consisted of beet roots, hay and oats). The values for the iodine content of bile obtained during fasting and that of bile examined immediately after the taking of food are widely different. This difference depends evidently on whether the bile is tested after fasting or after the ingestion of food. The values obtained after fasting have a rather narrow range (from 4 to 14 micrograms per hundred cubic centimeters of bile), being similar to those obtained for blood. The values for iodine obtained directly after eating are always higher (from 27 to 69 micrograms). Thus it is perfectly evident that the amount of physiologic iodine present in the bile at any given time will be greatly influenced by alimentation, which is diametrically opposed to the behavior of iodine in the blood. For example, in one instance bile examined three hours after eating gave values of 55 micrograms per hundred cubic centimeters of blood, but five hours later the values had fallen to 34 micrograms.

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[13] Elmer, A. W., and Luczynski, Z.: L'excrétion d'iode par la bile, à jeûne et après le repas, Compt. rend. Soc. de biol. **114**:1340, 1933.

In regard to the twenty-four hour excretion of iodine in the bile, the studies of Elmer and Luczynski gave values of from 2.8 to 26 micrograms during fasting and of from 20.7 to 82.2 micrograms after eating.

There is strong evidence, therefore, that the marked variations in the values for the iodine content of bile, their sudden and violent upward fluctuations, as noted by the aforementioned investigators, are influenced not only by seasonal and age conditions but by the time (fasting or after feeding) when the specimens to be tested are secured.

Finally, it must be admitted that the liver plays an important rôle in the metabolism of iodine and that immediately after food enters the digestive tract the liver acts to eliminate the iodine constituents by way of the bile.

In conclusion, Elmer and Luczynski proved that the amount of iodine in the bile is sharply influenced by alimentation. During fasting the values remain within comparatively narrow limits (from 4 to 14 micrograms per hundred cubic centimeters of bile). On the other hand, after eating the values rise sharply (as high as 69 micrograms). Therefore, the liver plays an important and immediate rôle in the metabolism of iodine.

The part played by the liver in the metabolism of iodine continued to interest Elmer and Luczynski,[14] for somewhat more than a year later a second note on their observations was published. They continued to study the behavior of iodine simultaneously in both blood and bile, in the fasting state and after the taking of food. In experiments on five rabbits, the iodine in the blood was estimated after a twenty-four hour fast. The iodine in the bile after fasting was not measured, but was estimated on the basis of median values derived from previous experiments on nine rabbits. The figures for the iodine content of the bile after fasting did not range between very wide limits; their minimum was 9.2 micrograms per hundred cubic centimeters of bile, closely approximating those for the iodine content of the blood.

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[14] Elmer, A. W., and Luczynski, Z.: Rôle du foie dans la régulation du taux de l'iode dans le sang, Compt. rend. Soc. de biol. **115**:1717, 1934.

After examinations were made of the blood during fasting, the animals were given a twenty-four hour alimentation of beet root, oats and hay. The bile was collected ninety minutes after the last feeding. At the same time a sufficient quantity of blood was obtained. The figures obtained show that the iodine content of the blood did not rise to any great extent (from a minimum of 13.2 micrograms up to 16.4 micrograms per hundred cubic centimeters of blood), while the iodine in the bile, on the contrary, showed a marked rise after the taking of food (from 9.2 micrograms to 45 micrograms).

It is evident that alimentary iodine is eliminated into the digestive tube, principally by the liver through the bile. In following up the fate of this iodine in the digestive canal, one is impressed by the fact that iodine appears in but very minute quantities in the stools. The amount of iodine excreted in the stools of experimental animals, all of which were on the same diet, varied from 2 to 11 micrograms in the twenty-four hours. The amount excreted in the bile far exceeds this, as the figures for iodine in the bile ranged between 32 and 82 micrograms in twenty-four hours.

One is forced to the conclusion that this divergence between the excretion of iodine in the stools and its excretion in the bile can be explained only by resorption by the blood stream of the iodine originally excreted into the digestive tube with the bile. The iodine thus enters the portal vein and completes a continually repeated cycle: from the digestive canal to the portal vein, from the portal vein to bile, from bile to the digestive canal and so on ad infinitum.

One might theorize that during the first stage of this cycle, when the iodine enters the circulation after a meal, the liver does not permit the iodine to accumulate in the blood until it reaches a high value; and that in proportion as the alimentary hyperiodemia (excess of iodine in the blood) is lowered, the iodine is once more resorbed into the digestive canal. Without doubt, the liver plays the part of regulator of the proportion of iodine in the peripheral blood in that it forces throughout the entire circulation the maintenance within comparatively narrow limits of a nicely adjusted balance of iodine in the blood.[14]

CLINICAL CONFIRMATION

The findings of these Polish investigators have been closely duplicated in my own clinic. In making our determinations we have used the method described by Trevorrow and Fashena[15] in 1935. As already stated, our original object was to obtain diagnostic aid in determining the extent of the thyrotoxicosis in our patients with goiter. We were sadly disillusioned after the idea had been put into practice for some time, because, although some patients suffering from hyperthyroidism did show an increase of iodine content of the blood, others—and the condition of some of them was as grave as that of any patients we have seen—gave values well within normal limits. This happened even when myxedema was in evidence. In our experience the results of the test for the iodine content of the blood in cases of goiter are sadly confusing when compared with the dependence we are able to place on the basal metabolism readings.

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[15] Trevorrow, V., and Fashena, G. J.: Determination of Iodine in Biological Material, J. Biol. Chem. **110**:29, 1935.

These findings have led us to the conclusion that iodine deficiency may not be the causative factor in the production of goiter, and the results obtained by others would seem to point in the same direction. The average ratio of inorganic to organic iodine in the cases in the clinic is 17 per cent. In reports from European clinics it averages 1:2. All our results emphasized the importance of the liver in the metabolism of iodine.

SUMMARY

The conclusion drawn from our studies and clinical applications was that determination of the iodine content of the blood might be a better test of hepatic function in cases of cholecystitis of long standing than the dye tests now in general use. This is because the liver is here working with a normal constituent of the blood, whereas when dyes are introduced artificially, as in the bromsulphthalein test, the introduction of a foreign element may well cause abnormal responses by the liver and disturb function appreciably. At present we are administering dextrose for several days before operation to all our patients with diseases of the gallbladder who have a high iodine content of the blood. This we believe to be far more effectual in preventing "liver deaths" than the administration of dextrose postoperatively. We have not yet been able to judge from the iodine content as to the most favorable time for performing operation, but are tentatively assuming that when it is below 100 micrograms per hundred cubic centimeters of blood one may operate with reasonable safety.

HEADACHE AFTER SPINAL ANESTHESIA

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Various explanations have been given for the postoperative headache which occasionally follows spinal anesthesia. Most of them can be classified under the headings of: (*a*) seepage of cerebrospinal fluid after spinal puncture,[1] (*b*) irritative meningitis[2] and (*c*) contamination of the material injected, causing irritation of nerve tissue.[3]

Recently considerable has been said regarding factors which render the anesthetic agent irritating to nerve tissue and thus produce postoperative headache.[3a] It has been claimed that contamination by antiseptic solutions used for sterilization of the skin (needle puncture through skin dripping with iodine) caused headache; also that hypertonicity resulting from dissolving crystals of procaine hydrochloride in cerebrospinal fluid was a potent factor in the production of headache. Further, it has been stated that the p_{H} of the solution is also important.

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1. (*a*) Peluse, S.: Post-Spinal-Anesthetic Headache, Illinois M. J. **67**:372, 1935. (*b*) Evans, C. H.: Possible Complications with Spinal Anesthesia: Their Recognition and Measures Employed to Prevent and to Combat Them, Am. J. Surg. **5**:581, 1928. (*c*) Nelson, M. O.: Postpuncture Headaches: A Clinical and Experimental Study of the Cause and Prevention, Arch. Dermat. & Syph. **21**: 615 (April) 1930. (*d*) Heldt, T. J.: Lumbar Puncture Headache, M. J. & Rec. **129**:136, 1929. (*e*) Weinstein, M., and McHugh, J. P.: One Thousand Cases of Spinal Anesthesia, ibid. **135**:507, 1932. (*f*) De Courcy, J. L.: New Methods of Controllable Spinal Anesthesia: The Use of Pitkin's Method in One Hundred Cases, Am. J. Surg. **5**:620, 1928. (*g*) Pitkin, G. P.: Spinal Anesthesia, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1935, vol. 1, chap. 5, pp. 22-23. (*h*) MacRobert, G.: The Cause of Lumbar Puncture Headache, J. A. M. A. **70**:1350 (May 11) 1918.

2. Stillwell, W. C.: Lumbar Anesthesia: Résumé of Seven Hundred and Fifty-One Cases, Minnesota Med. **15**:73, 1932. Anderson, E. R.: Complications of Spinal Anesthesia, Journal-Lancet **51**:73, 1932. Frazier, C. H.: Surgery of the Spine and Spinal Cord, New York, D. Appleton & Company, 1918. Parker, H. L.: Headache Following Diagnostic Spinal Puncture, Proc. Staff Meet., Mayo Clin. (supp. 1) **4**:369, 1929. Evans.[1b] Heldt.[1d] Pitkin.[1g]

3. (*a*) Harrison, P. W.: Postanesthetic Headache, Arch. Surg. **32**:99 (Jan.) 1936. (*b*) Babcock, W. W.: Spinal Anesthesia in Fact and Fancy, Surg., Gynec. & Obst. **59**:94, 1934. (*c*) Braun, H.: Localanesthesie, ed. 3, Leipzig, Johann Ambrosius Barth, 1914. Evans.[1b]

With a view to obtaining definite information regarding these assertions, we deliberately contaminated the solution made by dissolving procaine hydrochloride in cerebrospinal fluid by the addition of tincture of iodine and a solution of 2, 4, 6-trinitrophenol. We also compared the effects of using procaine hydrochloride dissolved in physiologic solution of sodium chloride, tap water and distilled water with procaine hydrochloride dissolved in cerebrospinal fluid.

METHOD

The experiment was conducted in five parts, twenty-five patients being used in each group. The anesthetic agent used was procaine hydrochloride, in doses of 150 mg. All the injections were made between the second and the third lumbar vertebra with as nearly the same force and speed as possible, in an attempt to secure uniformity of introduction into the subarachnoid space. The injections were made with the Labat needles (22 gage), which we always use for this type of procedure.[4] No attempt was made to discriminate between types of headaches or degrees of severity. If any headache was felt, it was recorded.

Table 1.—*Data on Postoperative Headache in Group 1 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	4/30	28	Appendectomy	None
2	5/10	25	Hernioplasty; appendectomy; resection of ovary	None
3	5/11	18	Appendectomy	None
4	5/12	37	Appendectomy; suspension of uterus	None
5	5/12	45	Appendectomy	None
6	5/14	55	Vaginal hysterectomy; perineorrhaphy	None
7	5/13	51	Excision of osteoma of foot	None
8	5/13	30	Amputation of cervix; interposition; Bell-Beattner operation; perineorrhaphy	None
9	5/13	27	Cholecystectomy; appendectomy	None
10	5/13	19	Appendectomy; oophorectomy on right	None
11	5/14	26	Open reduction for fractured patella	None
12	5/14	44	Hernioplasty	None
13	5/14	18	Appendectomy; resection of ovary	None
14	5/14	31	Hernioplasty	None
15	5/14	44	Cholecystectomy; appendectomy; suspension of uterus	None
16	5/14	37	Appendectomy	None
17	5/15	55	Bilateral hernioplasty	None
18	5/15	60	Exploratory operation for carcinoma of rectosigmoid region with metastasis to liver	Preoperative
19	5/16	34	Bilateral hernioplasty	None
20	5/16	33	Bilateral hernioplasty; hemorrhoidectomy	None
21	5/16	28	Bilateral hernioplasty	None
22	5/16	27	Left oophorectomy; appendectomy	None
23	5/16	21	Appendectomy	None
24	5/17	28	Excision of pilonidal cyst	None
25	5/17	32	Appendectomy	None

Group 1.—To 150 mg. of procaine hydrochloride dissolved in 4 cc. of cerebrospinal fluid, 1 minim (0.062 cc.) of tincture of iodine was added, and the resultant mixture was injected into the subarachnoid space. The operation was performed, and headache was awaited. The results are recorded in table 1.

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[4] Koster, H.: Spinal Anesthesia (with Special Reference to Its Use in Surgery of the Head, Neck and Thorax), Am. J. Surg. **5**:554, 1928. Koster, H., and Kasman, L. P.: Spinal Anesthesia for the Head, Neck, and Thorax: Its Relation to Respiratory Paralysis, Surg., Gynec. & Obst. **49**:617, 1929.

The patient in case 18 on whom an exploratory operation was done for carcinoma of the rectosigmoid region, had a preoperative frontal headache for several days. At operation, miliary peritoneal and hepatic metastases were found. Postoperatively the patient continued to complain of frontal headache. Weeks subsequently there developed personality changes, an increase in intracranial pressure and ocular changes, all indicative of cerebral metastasis.

Group 2.—To 150 mg. of procaine hydrochloride dissolved in 4 cc. of cerebrospinal fluid, 1 minim of a solution of trinitrophenol (6 per cent trinitrophenol in 60 per cent alcohol) was added, and the resultant mixture was injected into the subarachnoid space. The operation was then performed, and headache was awaited. The results appear in table 2.

Two patients in this series complained of headache postoperatively.

TABLE 2.—*Data on Postoperative Headache in Group 2 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	5/18	29	Left salpingectomy; appendectomy...........	None
2	5/18	28	Hemorrhoidectomy...........................	None
3	5/18	66	Interposition; perineorrhaphy................	None
4	5/18	13	Appendectomy..............................	None
5	5/18	40	Appendectomy; separation of pericholecystic adhesions..................................	None
6	5/19	33	Cholecystectomy; sterilization; appendectomy	None
7	5/19	43	Supracervical hysterectomy; appendectomy...	2 days
8	5/19	53	Choledochostomy; cholecystectomy; appendectomy..................................	None
9	5/19	39	Supracervical hysterectomy; oophorectomy; appendectomy.............................	None
10	5/19	32	Supracervical hysterectomy; left oophorectomy......................................	None
11	5/19	43	Supracervical hysterectomy; oophorectomy...	None
12	5/19	24	Hernioplasty; appendectomy.................	None
13	5/19	16	Appendectomy..............................	None
14	5/19	51	Panhysterectomy; appendectomy.............	None
15	5/19	35	Cholecystectomy; appendectomy; sterilization..	3 days
16	5/20	36	Appendectomy..............................	None
17	5/20	44	Supracervical hysterectomy; oophorectomy; appendectomy.............................	None
18	5/20	53	Hemorrhoidectomy..........................	None
19	5/20	24	Appendectomy..............................	None
20	5/20	24	Appendectomy; resection of ovary...........	None
21	5/21	11	Appendectomy..............................	None
22	5/21	35	Cholecystectomy; appendectomy.............	None
23	5/23	39	Cholecystectomy; appendectomy.............	None
24	5/22	36	Hernioplasty................................	None
25	5/22	17	Appendectomy..............................	None

Group 3.—One hundred and fifty milligrams of procaine hydrochloride was dissolved in 4 cc. of sterile physiologic solution of sodium chloride, and the resultant mixture was injected into the subarachnoid space after 4 cc. of cerebrospinal fluid was withdrawn. The results as regards postoperative headache are shown in table 3.

Only one patient in this group complained of headache postoperatively.

Group 4.—One hundred and fifty milligrams of procaine hydrochloride was dissolved in 4 cc. of sterile tap water, and the resultant mixture was injected subarachnoidally after 4 cc. of cerebrospinal fluid was withdrawn. The results as regards headache are shown in table 4.

Two patients in this group had headache postoperatively.

TABLE 3.—*Data on Postoperative Headache in Group 3 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	6/ 4	19	Appendectomy	None
2	6/ 4	47	Hernioplasty	None
3	6/ 5	35	Cholecystectomy; appendectomy	None
4	6/ 5	48	Supravaginal hysterectomy	1 day
5	6/ 8	42	Thyroidectomy	None
6	6/ 6	29	Cauterization of cervix; tracheloplasty	None
7	6/ 8	26	Closure of gastrocolic fistula	None
8	6/ 6	13	Appendectomy; resection of ovary	None
9	6/ 7	45	Supracervical hysterectomy; appendectomy	None
10	6/ 7	16½	Appendectomy	None
11	6/ 7	25	Appendectomy	None
12	6/ 8	53	Perineorrhaphy; Kelly's plication of urethra	None
13	6/ 8	18	Appendectomy	None
14	6/ 8	35	Perineorrhaphy; myomectomy; oophorectomy; appendectomy; hemorrhoidectomy	None
15	6/ 8	25	Appendectomy	None
16	6/ 9	33	Repair of anterior and posterior wall; supracervical hysterectomy	None
17	6/ 9	57	Appendectomy	None
18	6/10	21	Salpingectomy for ectopic pregnancy; appendectomy	None
19	6/10	57	Vaginal hysterectomy; perineorrhaphy	None
20	6/11	32	Left salpingo-oophorectomy; appendectomy; suspension of uterus	None
21	6/11	27	Cholecystectomy; appendectomy	None
22	6/11	20	Appendectomy	None
23	6/11	32	Supracervical hysterectomy; oophorectomy; appendectomy	None
24	6/11	32	Appendectomy	None
25	6/11	16	Appendectomy	None

TABLE 4.—*Data on Postoperative Headache in Group 4 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	5/26	58	Splenectomy	None
2	5/26	61	Gastrectomy; Murphy's button gastro-jejunostomy	None
3	5/26	29	Hernioplasty	None
4	5/26	36	Left oophorectomy	2 days
5	5/26	20	Bilateral hernioplasty	None
6	5/26	25	Myomectomy suspension; oophorectomy	2 days
7	5/26	43	Perineorrhaphy	None
8	5/27	46	Supracervical hysterectomy; appendectomy	None
9	5/26	11	Appendectomy	None
10	5/27	34	Supracervical hysterectomy; cholecystectomy; appendectomy; oophorectomy	None
11	5/26	42	Appendectomy	None
12	5/29	33	Hernioplasty; appendectomy	None
13	5/29	35	Hernioplasty; appendectomy	None
14	5/29	30	Bilateral oophorectomy; appendectomy	None
15	5/29	29	Appendectomy	None
16	5/29	41	Excision of pilonidal cyst	None
17	5/29	36	Hernioplasty (Gallie's)	None
18	5/30	59	Hernioplasty, incarcerated femoral	None
19	5/31	35	Bilateral oophorectomy; appendectomy	None
20	6/ 2	22	Hernioplasty, scrotal	None
21	6/ 2	62	Hernioplasty, scrotal	None
22	6/ 2	4½	Hernioplasty, inguinal	None
23	6/ 2	30	Appendectomy	None
24	6/ 3	30	Diagnostic curettage for carcinoma of uterus	None
25	6/ 3	47	Supracervical hysterectomy; oophorectomy; hemorrhoidectomy	None

Group 5.—One hundred and fifty milligrams of procaine hydrochloride was dissolved in 4 cc. of distilled water, and the resultant mixture was injected subarachnoidally after 4 cc. of cerebrospinal fluid was withdrawn. The results as regards postoperative headache are shown in table 5.

TABLE 5.—*Data on Postoperative Headache in Group 5 After Spinal Anesthesia*

Case	Date	Age	Operation	Headache
1	7/13	57	Separation of adhesions..........................	None
2	7/13	50	Supracervical hysterectomy; appendectomy...	None
3	7/13	25	Appendectomy; hemorrhoidectomy...........	None
4	7/13	37	Appendectomy................................	None
5	7/13	11	Appendectomy................................	None
6	7/13	24	Appendectomy................................	None
7	7/14	37	Appendectomy; sterilization; myomectomy...	None
8	7/13	19	Appendectomy................................	None
9	7/14	47	Hernioplasty................................	None
10	7/14	66	Resection of sigmoid colon....................	None
11	7/15	60	Exploratory; biopsy..........................	None
12	7/16	36	Exploratory; appendectomy..................	None
13	7/15	34	Supracervical hysterectomy; right oophorectomy; appendectomy........................	None
14	7/14	15	Appendectomy................................	None
15	7/15	21	Appendectomy; resection of ovary............	None
16	7/16	65	Hernioplasty................................	None
17	7/16	40	Supracervical; hysterectomy; oophorectomy; appendectomy..............................	None
18	7/15	19	Appendectomy................................	None
19	7/15	45	Appendectomy:................................	None
20	7/15	54	Resection of intestine (ileitis)...	None
21	7/16	21	Repair of hydrocele...........................	None
22	7/16	26	Appendectomy................................	None
23	7/17	27	Appendectomy................................	None
24	7/17	54	Excision of varicosities........................	None
25	7/18	36	Appendectomy; myomectomy; sterilization; perineorrhaphy; biopsy of intestine.........	None

COMMENT

In an editorial by one of us[5] concerning the criteria of scientific proof, the point was made that uncontrolled biologic phenomena could not be used as significant data unless the material represented large values numerically. Thus it was shown that in our clinic, where spinal anesthesia was used as a routine for all major operations, as many as a hundred consecutive patients would frequently be anesthetized in this manner without a single instance of postoperative headache occurring, and then without any recognizable departure from the routine previously used, four or five subsequent patients would have headache. With one of these groups of one hundred headache-free patients as the criterion, it could have been said that the technic employed obviated the occurrence of postoperative headache. These next four or five patients would have demonstrated how erroneous the conclusion was. In a controlled series, however, in which individual factors are tested, comparatively small numbers can give significant results.

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[5] Koster, H.: Evaluation of the Results of Treatment, Am. J. Surg. **20:** 157, 1933.

It seems hardly likely that contamination of injected fluid with iodine could produce postoperative headache. Iodine precipitates procaine hydrochloride, and this reaction is the basis for one of the chemical tests for procaine hydrochloride. Therefore, the iodine itself could not act as an irritant. If the insoluble compound formed by iodine and procaine hydrochloride is the irritating factor, then it must be very potent, since the amount of iodine which could be carried by the tip of the needle from dripping skin through approximately 3 inches (7 cm.) of tissues before the arachnoid is reached must be very small—certainly a minute fraction of a minim. The failure to produce headache uniformly in the twenty-five cases in which the solution of procaine hydrochloride was deliberately contaminated with 1 minim of tincture of iodine suggests strongly that contamination with iodine is not a potent factor in the development of postoperative headache after spinal anesthesia.

In our clinic, where spinal anesthesia has been induced in approximately 11,000 instances in the past eleven years, a solution of 6 per cent trinitrophenol in 60 per cent alcohol has been used for preparation of the skin. If contamination by solutions used for this preparation is responsible for headache, then in our cases it must have been either the trinitrophenol or the alcohol which was the contaminant. However, the failure to produce headache uniformly in the twenty-five cases in which one minim of solution of trinitrophenol was deliberately added to the anesthetic agent injected again suggests strongly that it is not a causal agent.

The relation of hypertonicity to the development of postoperative headache has never been demonstrated. The experiments with saline solution and water as solvents for procaine hydrochloride have failed to yield any significant information, and it must be conceded that from the data it cannot be concluded that postoperative headache depends on the hypertonicity or the hypotonicity of the injected solution.

No reliable data concerning the effect of varying the p_H on the development of postoperative headache are available. The p_H[6] of cerebrospinal fluid plus procaine hydrochloride is 7; that of tap water and procaine hydrochloride is 5.93, and that of distilled water plus procaine hydrochloride is 5.63. After the injection of procaine hydrochloride dissolved in distilled water, headache was not uniformly produced. However, that is not surprising when it is remembered that only 4 cc. of the procaine hydrochloride solution is injected into a fluid the minimum amount of which is at least 50 cc. and which contains considerable buffer substance. As a matter of fact, if three minutes after the injection of 4 cc. of distilled water containing 150 mg. of procaine hydrochloride into the subarachnoid space a sample of cerebrospinal fluid is withdrawn, it is found to have a p_H of 7.

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[6] The p_H determinations were made with a glass electrode.

It can be seen from the tables that if the one patient in group 1 who had a headache preoperatively is left out of the consideration, there were five patients with postoperative headache among the one hundred who were used in the experiments. The ordinary incidence of postoperative headache in our experience is 5 per cent.

The experiments were carried out on the first four groups of patients consecutively. There was an interval between the experiments on group 4 and group 5, during which time one hundred and thirty-five persons were anesthetized with procaine hydrochloride dissolved in cerebrospinal fluid. Of this number, not a single person had headaches postoperatively.

CONCLUSIONS

1. The addition of either tincture of iodine or a solution of trinitrophenol to procaine hydrochloride dissolved in cerebrospinal fluid does not add to the risk of development of headache postoperatively.

2. Hypotonicity or hypertonicity as occasioned by using tap water, saline solution or distilled water also is not a factor in the production of headache postoperatively.

3. Buffer substances are present in cerebrospinal fluid in sufficient quantities to render innocuous ordinary solutions used to develop anesthesia which might have a p_H as low as 5.63.

INTESTINAL OBSTRUCTION

AN ATTEMPT AT AN IMPROVED DISCUSSION OF ITS PATHOLOGIC PHYSIOLOGY AND TREATMENT BASED ON A SIMPLE CLASSIFICATION AND ON PAST EXPERIMENTAL AND CLINICAL EXPERIENCE

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In 1933, in conjunction with Dr. B. F. Stout, I initiated some experiments on intestinal obstruction. Since that time continued experimental and clinical work on this problem have contributed toward a conception of this disease which is more comprehensive and proper than the conception we previously held.

We have been encouraged by others to believe that certain phases of our previous work, which will be discussed briefly later in this paper, may have been of some value in clarifying somewhat one fundamental aspect of the condition.[1] I venture to present here a simplified classification of intestinal obstruction which I feel is amenable to a comprehensive, yet brief and improved, discussion of its known pathologic physiology. The majority of the points mentioned have been previously reviewed by others. Certain aspects of the classification and discussion, however, have not.

It must be admitted that a perfect classification of any disease is impossible as long as there are unsolved aspects of it, and certainly there is more to be learned about obstruction. The importance of an impaired blood supply in cases of obstruction has not been as widely appreciated as it should have been because of the confusion attending the many theories and discussions which have been carried on over the world regarding unknown aspects of obstruction. In accepting the importance of the impaired blood supply as I do in the following discussion, I do so on the basis of the work of Kader, Murphy and Vincent, Gatch, Gatch and Culbertson, McIver, Wilkie and many others. The importance of this factor has been proved beyond question. It must be acknowledged that investigators do not know the exact mechanism of the deleterious action of an impaired blood supply. It

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[1] Donaldson, J. K., and Stout, B. F.: Mesenteric Thrombosis: Arterial and Venous Types as Separate Clinical Entities, Am. J. Surg. **29**:208 (Aug.) 1935.

may, furthermore, be acknowledged that there may be some legitimate dispute as to the primary importance of neurogenic and other factors in distention associated with obstruction. From a practical standpoint, however, one is justified in accepting any hypothesis as a working basis as long as this hypothesis procures end-results which are as good as, or superior to, any other end-results. The following trend of thought will at present procure these results.

In accepting the theory that distention may produce sufficient ischemia of the mucous membrane of the intestine to cause a lethal absorption of toxin, one accepts dogma which has good support. Gatch and Culbertson [2] are the latest workers to offer evidence in this direction. It probably would be unfair to say that other influences never play a part in distention. It seems probable, however, that when distention is the cause of death, as it sometimes is, it is always sufficiently marked to interfere with the blood supply to the mucous membrane, even though other factors may possibly enter into the picture. As far as present day knowledge is concerned, however, the proper treatment is the same whether or not one chooses to accept the factor of an impaired blood supply in distention as one of the main factors in the morbid picture.

Classification of Intestinal Obstruction *

I Direct Obstruction of the Lumen		II Indirect Obstruction of the Lumen	
1. With primary interference with blood supply	2. Without primary interference with blood supply	1. With primary interference with blood supply	2. Without primary interference with blood supply
a (a) Folded strangulated loop in cavity	a (c) Simple high or low obstruction with no folded loop	a (e) Occlusion of mesenteric arteries without direct obtion of lumen	a (g) Postoperative ileus
b (b) Strangulated loop isolated from cavity, as in incarcerated hernia	b (d) High or low obstruction with added obstruction of folded loop	b (f) Occulsion of mesenteric veins without direct obstruction of lumen	b (h) Ileus from acute infectious disease or from other causes without direct obstruction of lumen

* It is to be acknowledged, of course, that for academic completeness subclassifications dealing with the wide variety of specific causes of obstruction should be added to this classification. These details of subclassification, however, should not be confused with the fundamentals of pathologic physiology with which the classification given here deals.

THE TWO CHIEF CONCERNS IN OBSTRUCTION

Before referring to the classification in the table, I am assuming, then, with the possible reservations mentioned previously, that in practically all cases of obstruction there are two main problems. 1. The first one is the potential loss of fluid and salts. The seriousness of this factor is widely appreciated and needs no further consideration for the moment. 2. The second is potential interference with the blood supply to the intestine, either by primary interference or by interference secondary to distention. The physiologic relationship of other factors to these two highly important ones will be discussed later.

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[2] Gatch, W., and Culbertson, C. G.: Circulatory Disturbances Caused by Intestinal Obstruction, Ann. Surg. **102:**619 (Oct.) 1935.

The classification of intestinal obstruction appears in the accompanying table.

It may be noted that all types of obstruction are divided into two large classes: (I) that in which there is an actual direct blockage of the lumen of the intestine, such as may rise, for example, from an adhesion or from an intra-intestinal or extra-intestinal foreign body or tumor, and (II) that in which the lumen of the intestine is indirectly obstructed but not closed, as in postoperative ileus. These two main divisions are further divided into two groups on the basis of one of the two chief concerns in obstruction, namely, the blood supply: (1) that group in which the blood supply is primarily interfered with and (2) that in which the blood supply is not primarily interfered with but in which it may be secondarily threatened by distention. On the simple foundation of these parts of the classification, one can rapidly build an understanding of diagnostic and therapeutic considerations. Before proceeding, however, with further discussion of the relation of secondary factors a brief consideration of certain differences caused by strangulation of the arterial supply as against an uncomplicated strangulation of the venous return from the intestine should be given.

NECESSITY FOR APPRECIATING THE DIFFERENCE BETWEEN ARTERIAL AND VENOUS MESENTERIC OCCLUSION

The differences between pure venous mesenteric occlusion and arterial mesenteric occlusion have a bearing on the fundamental physiology of obstruction as a whole. Previous to 1934 or 1935 it seemed to have been generally accepted that the end-results of occlusion of the mesenteric veins and those of occlusion of the mesenteric arteries were the same. Mention had been made of the anatomic difference of the two types, but a full realization of the pathologic differences between the two had never, as far as I know, been appreciated previous to the work of Dr. Stout and myself on this subject.[3] The opinions expressed in our published reports have been confirmed or at least upheld by others since that time. Ochsner has referred to clinical cases of purely venous thrombosis of the mesenteric vessels in which recovery occurred without resection. Certain parts of the work done by Knight and Slome[4] evidently gave results similar to ours.

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[3] Donaldson, J. K., and Stout, B. F.: Mechanics of Absorption in Intestinal Obstruction, Texas State J. Med. **30**:455 (Nov.) 1934. Donaldson and Stout.[1]

[4] Knight, G. C., and Slome, D.: Intestinal Strangulation, Brit. J. Surg. **23**:821, 1936.

Held and Goldbloom[5] reported a case of venous thrombosis of the mesenteric vessels following repeated administration of phenolphthalein. So it seems an established fact that there are vast pathologic and clinical differences between pure venous occlusion of the mesenteric vessels and pure arterial occlusion, provided the lumen of the intestine remains sufficiently unobstructed in the former. Occlusion of some of the mesenteric veins does not always cause secondary arterial thrombosis; it does not necessarily cause gangrene of intestinal tissue if the intestinal lumen remains sufficiently patent to empty the involved loop of collecting fluids, and it does not per se cause paralytic ileus; it does give rise to a different clinical picture than that produced by arterial occlusion. Failure to realize these facts has been responsible for some misinterpretation of the problem of obstruction. For example, statements of good surgeons have depreciated to a certain extent the danger of gangrenous intestine, cases being cited in which, after resection of a loop of blackened intestine which had evidently been present for days, the patient recovered. Likewise, it has been said that the omentum and the peritoneum will often wall off a gangrenous loop of intestine in the peritoneal cavity, thereby decreasing the danger. The latter mechanism and result may take place in a case of incarcerated hernia, but the tremendous fulminating danger of gangrene should never be minimized. Unquestionably confusion of the loops of blackened but not gangrenous intestine which occur in cases of venous occlusion with truly gangrenous loops in cases of arterial occlusion has been responsible for some misunderstanding. I have often seen experimentally a blackened intestinal loop in a case of purely venous occlusion which "walled off," with resulting clinical recovery, but I have never seen true gangrene of the intestine in an animal or in man go through a similar process to successful recovery. Such an incident, if it occurs at all, must be extremely rare.

MECHANISM OF THE SECONDARY FACTORS

The mechanism of the secondary factors of intestinal obstruction, as outlined in the table, are discussed briefly.

a (*c*). In the simple type of obstruction in which no direct interference with the blood supply is present, what is the mechanism of the developing pathologic process? If the obstruction is high it is generally known that vomiting with loss of fluid and salts rapidly supervenes and may be the most important part of the picture. Distention may not develop, because the unobstructed intestine may automatically regurgitate through the pylorus. Consequently, interference with the blood supply may not occur.[6] In this type of obstruction infusions of saline solution, combined with decompression by the use of the Wangensteen or nasal catheter if distention is present, will give immediate temporary relief. Obstruction has righted itself after such treatment. Temporization carries, however, the responsibility of assuming surety as to type of obstruction.

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[5] Held, I. W., and Goldbloom, A. A.: Three Rare Intra-Abdominal Cases, S. Clin. North America **14**:389 (April) 1934.

If the simple obstruction is lower in the small bowel, serious vomiting will develop later. Distention of the intestine will appear, eventually interfering with the blood supply to the mucous membrane. Distention will be harder to control by decompression through the nasal catheter because of the loops of intestine folding on themselves.

If the simple obstruction is in the large bowel, vomiting will become a serious factor only late in the disease, if ever. Distention in the large bowel may not cause the production or absorption of toxin directly but may cause a rupture of an ischemic area in the cecum, even before serious subjective symptoms have presented.[7]

b (*d*). If the obstruction is of the looped type in which the bowel is folded on itself, obstructing a segment as well as the main continuity of the intestine, there is immediately superimposed on the consideration as to the level of obstruction the added factor of the obstructed loop. This loop may rapidly become distended, bringing ischemia to its mucous membrane or additional constriction to its primary blood supply. Temporization procedures in this type are extremely dangerous.

a (*a*). If one has a gangrenous loop of intestine free in the peritoneal cavity anywhere, its level is of secondary consequence. Unless the area of gangrene is removed promptly from the cavity, death will follow. With a folded loop, however, in which there is interference with the blood supply, one should realize the different pathologic pictures which may be produced by purely venous occlusion as against arterial occlusion. As previously stated, every blackened intestinal loop is not gangrenous. Also, there is a difference between the advancing pathologic condition in a folded loop to which the venous apparatus and and the lumen are both occluded and that of an intestine in which the veins supplying it are closed with the intestine not occluded. In the former the collection of fluid and distention of the intestine are rapid, with tremendous bacterial proliferation and interference with the arterial supply soon presenting.

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[6] Jenkins, H. P., and Beswick, W. F.: Prolongation of Life for Seventy Days in High Intestinal Obstruction by Administration of Sodium Chloride and Nutritive Material Below the Site of Occlusion, Arch. Surg. **26**:407 (March) 1933.

[7] Saeltzer, D. V., and Rhodes, G. K.: Diastasic Perforation of the Normal Cecum, Ann. Surg. **101**:1257 (May) 1935.

b (*b*). If a strangulated loop is isolated within an incarcerated hernia so tightly that no absorption through the mesentery or peritoneal cavity can occur, it is for the moment, to an extent, a simple obstruction. In operating for this type of obstruction one should be extremely careful when gangrenous intestine is freed from the incarceration to prevent its toxic content from moving into the lumen of the intestine remaining in the peritoneal cavity, if the latter bowel is damaged at all by distention. Otherwise a severe dose of toxin may be absorbed.

a (*e*). In obstruction occurring from paralysis secondary to arterial mesenteric occlusion in which no direct obstruction of the lumen is present, one is, as with gangrenous intestine of other types, concerned only with immediate operation.

b (*f*). If the occlusion of the vessels is purely of the venous type without obstruction of the lumen, the clinical course which has been described by Dr. Stout and myself [1] may possibly end in recovery if the involvement of the intestine is not too extensive. Prompt surgical intervention, however, is probably, as a rule, the treatment of choice.

a (*g*) and *b* (*h*). In the last two groups, in which a primary paralytic ileus is present, as for example in acute infectious diseases or in the primarily paralytic postoperative type, abdominal exploration is not indicated. Other decompression measures may be life saving.

The differential diagnosis of the foregoing types of obstruction will not be discussed here. There are points of difference between all types. It can readily be seen how complicated the differential picture between many of them usually would be, however, if the diagnosis were to be made early and with surety. Furthermore, general statistics reveal that operation for simple obstruction within twenty-four hours after the onset produces a low mortality. The mortality is still lower if operation is done earlier. For the gangrenous types, as previously stated, the most prompt surgical intervention possible is essential. Absorption of toxin probably starts within thirty minutes after the blood supply is strangulated.[4] If operation is delayed more than twelve hours after the onset of gangrene, a very high death rate is to be expected. I know of no mortality statistics which subdivide the twelve hour period in reference to gangrene, but I feel that with every single hour's delay after gangrene supervenes the mortality is increased.

So when one keeps in mind the different pathologic pictures of obstruction, the difficulty of an early clinical differentiation between most of them and the mortality statistics as related to early operation in most types of the disease, it is easy to understand the grave responsibility one assumes when one uses temporization measures to postpone operation in all but the primary paralytic types, as listed in *a* (*g*) and *a* (*h*) or sometimes in *b* (*f*) of the classification. Fortunately, these types are fairly easily differentiated from the others.

SUMMARY

A discussion of the pathologic physiology and treatment of intestinal obstruction as based on a simple classification is presented. The majority of the points in this discussion have been previously mentioned, but certain aspects of it are offered as an improvement over some conceptions formerly held.

Previous experimental and clinical work citing differences in the pathologic picture of the arterial and of venous types of mesenteric occlusion are discussed. These differences as they are related to certain fundamentals of the problem of obstruction as a whole should be more fully appreciated.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomalies.—Shih and Char[1] stated that congenital solitary kidney may be defined as an anomalous condition in which one kidney is absent because of a disturbance of growth of the nephrogenic tissue in embryonic life and the existing kidney has developed from one renal bud. If the solitary kidney is healthy, congenital absence of the opposite kidney does not give rise to pathognomonic symptoms, and the condition may exist for years without the patient being aware of it.

It cannot be overemphasized that recognition of solitary kidney is of paramount importance and should merit the great concern of the urologic surgeon. A congenital solitary kidney is compatible with normal physiologic function, and a patient with this anomaly maintains full working capacity. The condition is of clinical significance only in the presence of renal disease.

Operation should be recommended only when it is absolutely imperative, and surgical procedures should be as conservative as possible. Experience has demonstrated that the risk of operation on the solitary kidney varies directly with the impairment of function and the degree of infection and that delay in operating on a solitary kidney until urinary obstruction or anuria has developed definitely increases the operative mortality. In the presence of good renal function and in the absence of infection, a great variety of surgical procedures have been and may be performed on the solitary kidney, with gratifying results.

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[1] Shih, H. E., and Char, G. Y.: Congenital Solitary Kidney, Chinese M. J. **50**:821-826 (June) 1936.

This anomaly is of interest from the standpoint of its genesis and of importance because of its significance to the patient. This condition, even though it is infrequent, should be kept in mind by all those who are interested in surgical treatment of renal conditions.

Char, Shih and Wen [2] reported 14 cases of duplication of the kidney and ureter. The pathologic picture, symptomatology, diagnosis, prognosis and treatment were considered. The authors pointed out that the complicating pathologic lesion may be found in either the ectopic or the normal segment of the kidney, in spite of the general belief that the upper ectopic segment is usually the seat of disease. From clinical and embryologic studies, it is concluded that as long as proper connections exist between the supernumerary kidney and its ureter it is capable of the functions of a normal organ. Their findings tend to endorse the view that these anomalies develop as a result of a separate outbudding from the mesonephric duct or as a bifurcation of the original ureteral bud.

Mayers [3] stated that congenital displacement is to be distinguished from acquired displacement of the kidney. Marked displacement of congenital origin is uncommon. One of the rarest types is a condition in which both kidneys are on the same side of the body. There is a similarity between various forms of displacements and anomalies of structure which often causes confusion in the terminology; for example, a horseshoe kidney which is situated entirely on one side of the midline is identical with a fused type of crossed renal ectopia.

The embryologic factors involved were considered. There are two chief schools of thought: (1) that which believes displacement is due to failure of ascent of the kidney and (2) that which believes that it is attributable to descent of the kidney. Both schools believe that the mechanism involved is closely related to the process of vascularization and that other related factors are variations in the location and branching of the ureteral bud. The marked forms of displacement occur early in embryonic life.

The fused type of crossed renal ectopia is perhaps ten times more frequent than the unfused type. A search of the literature revealed reports of 19 cases which were in all probability true cases, or cases of the unfused type, of crossed renal ectopia. Undoubtedly many other cases which have been reported in the literature as of the fused type may be of the unfused type. Mayers reported 7 such cases.

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[2] Char, G. Y.; Shih, H. E., and Wen, I. C.: Duplication of the Kidney and Ureter, J. Urol. **36**:305-326 (Oct.) 1936.

[3] Mayers, M. M.: Crossed Renal Ectopia, J. Urol. **36**:111-122 (Aug.) 1936.

Nineteen cases of crossed renal ectopia, not including the 7 reported by Mayers, presented the following characteristics: In 8, the patients were women, and in 10, men; in 1 case the sex was not reported. The right kidney was involved in 3 cases, the left in 15 cases and both in 1 case. The crossed kidney was under the uncrossed kidney in 17 cases and over the uncrossed kidney in 1 case. In 1 case both kidneys were crossed.

Mayers added to those reported in the literature 1 case in which the condition bore all the characteristics of an unfused type of crossed renal ectopia. The patient was a man whose right kidney was uncrossed and whose left kidney was crossed over and placed under the right. There was pyelitis of both kidneys, and the right kidney contained three large calculi. Diagnosis was made by examination and confirmed at operation. This case is unique as calculi were present in the uncrossed partner of the combination. As far as Mayers could determine, there is no other case reported in the literature in which this situation exists.

Lower[4] described a case of fused kidney in which three almost distinct kidneys had fused into one mass; two of these were in essentially normal position and were joined together by a third kidney lying medially and horizontally in front of the spinal column. This third kidney had a complete pelvis and a ureter, which anastomosed with the ureter of the left kidney at about its middle third. This median supernumerary kidney, which thus constituted the isthmus of a horseshoe kidney fused at the top, was removed with its anomalous ureter, leaving the patient with a right and a left kidney, both of which were functioning well, as was revealed by a postoperative intravenous urogram.

The author, who has had a series of 23 cases of fused kidney, pointed out that extreme care must be taken in establishing the diagnosis in such cases, because the symptoms are so largely referable to the gastro-intestinal tract as to be misleading. Many erroneous diagnoses of acute or chronic appendicitis, gallstones, duodenal ulcer, chronic ulcerative colitis and tumor of the colon have been made by practitioners who did not think of the possibility of horseshoe kidney and hence did not employ urography and the complete laboratory facilities to clear up the diagnosis.

The cardinal symptoms of horseshoe kidney, as summed up by Gutierrez, are umbilical or epigastric pain, extending to the lumbar region, chronic constipation and perhaps other gastro-intestinal disorders, and urinary disturbances associated with early signs of nephritis. These symptoms are attributable to the pressure exerted by the horseshoe kidney lying across the spine and close to the great abdominal vessels, the solar plexus and the abdominal sympathetic and parasympathetic nerves.

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[4] Lower, W. E.: The Problem of the Fused Kidney, J. Urol. **35:**588-595 (June) 1936.

A complete history should be taken with special reference to subjective as well as to objective symptoms. A tumor situated in the midline may be palpable and is often tender, and pain produced on bending backward sometimes will suggest the presence of a horseshoe kidney. Laboratory studies of the blood and urine should be made. A roentgenographic examination is essential, and this may give the first indication that a horseshoe kidney is present. The important points in establishing a diagnosis from roentgenograms are the outline and position of the kidney, the possible delineation of the isthmus, abnormalities in the shape and contour of the pelvis and calices (the lowermost calices usually point inward toward the midline), the abnormal position of the ureters, which in the horseshoe kidney usually enter the lateral and not the internal aspect of the renal organ, and, finally, any shortening of the ureters, stricture or kinking. The diagnosis is made easier if the kidney contains stones, since if multiple wedge-shaped calculi are present the direction of the axis of the kidney can often be determined from the way the stones are placed.

When symptoms are so severe that the patient seeks aid, an indwelling catheter should be inserted at once to secure drainage and to relieve infection; rest in bed, administration of urinary antiseptics and cathartics and intravenous injection of physiologic solution of sodium chloride should also be employed. Permanent cure can be obtained, however, only by surgical intervention, consisting of division of the isthmus with or without nephropexy, according to the degree of motility of the kidneys.

Ptosis.—Gouverneur and Cachin [5] stated that most of the poor results from operations on movable kidlneys in the past have been caused by a failure to recognize the correct indications. The mere presence of a movable kidney, with pain, was enough to invite operation, without any inquiry about the morphologic condition of the pelvis, ureter and kidney or the amount of infection in the urinary tract. The authors insisted on the paramount importance of taking retrograde ureteropyelograms with the patient in the vertical position and of taking into consideration the site of the pain, which shows the true position of the kidney, the form of the pelvis and, especially, the topography of kinks of the ureter.

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[5] Gouverneur, R., and Cachin, Charles: Le traitement chirurgical des ptoses rénales: Indications; technique; résultats, J. de chir. **47**:754-770 (May) 1936.

They have operated on 28 patients with movable kidney associated with marked functional troubles. The results, both anatomic and functional, were always excellent. In all but 5 cases retrograde ureteropyelograms were taken, the intravenous method of urography being used. It requires more delicate judgment to recognize the indications for operation than to perform the operation, for the technic is very simple. The patient should be studied for some time before the operation, as there is no need for hurry; several examinations should always be made. One should not operate on a patient with several other operative scars, for renal ptosis may be only the most apparent element of some general disease. Mild pyelonephritis in a ptotic kidney is an indication for operation; when a long course of treatment does not result in improvement, operation is indicated, and if the condition is a frank pyelonephritis, this is all the more true. Pyuria, which is not too excessive, is another indication for operation. If hydronephrosis is present, one must make sure that this is secondary to the ptosis and not a congenital condition, for in the latter case reposition will do no good.

At operation, the authors advocated high reposition. Despite some opinions to the contrary, their films revealed good results from this method. The old technics of Guyon and Albarran are inadequate, and yet they are the ones most frequently used. The incision used by Gouverneur and Cachin is slightly different from the usual lumbotomy; it is shorter, commences a little above and internal to the anterosuperior iliac spine and goes obliquely toward the costolumbar angle; two fingerbreadths below this it becomes vertical and continues directly upward to the tenth rib. It is only during the course of the operation that the situation of the kidney can be learned exactly, for it depends on the morphologic relations of the ribs, the thorax and the bed of the kidney. In effecting fixation, the linen threads are drawn from below upward and from within outward through the diaphragm, the two leaflets of the diaphragmatic pleura and the intercostal pleura and the intercostal muscles. A fault to avoid is that of passing the threads which have gone through the intercostal space and the diaphragm outward from the kidney bed; this can easily happen and will result in allowing the kidney to come only partially upward; the left hand placed under the cupola must serve as a guide to the needle. The sutures are tied two and two, the anterior together and the posterior similarly; the assistant in the meantime pushes the kidney into its bed and supports the lower pole. A small suspensory hammock is made for the lower pole of the perirenal fat and the lower part of the renal fascia and is tied above the twelfth rib or sometimes even above the eleventh rib. The patient should be kept in bed for three weeks, after which a course of exercises should be prescribed to strengthen the abdominal muscles.

Smith, McKim and Rush[6] reported their findings after a study of 238 nephropexies performed on 204 patients in the fourteen years prior to 1934.

They stated that there are four factors in ptosis of the kidney that may be of importance in the production of symptoms: 1. Tension on, and torsion of, the renal pedicle usually causes a sensation of heaviness and weight in the side affected and frequently interferes with the return flow of blood through the renal vein to such an extent as to produce attacks of renal colic in patients in whom there may be no evidence of renal stasis.

2. The excessive stimulation of the sympathetic nerves as a result of the constant pull on the splanchnic area may manifest itself in many ways and probably plays a rather important rôle in the production of the symptoms of the dyspepsia so frequently found in these cases. The frequency of intense headaches and of pain that is referred to a point midway between the scapulae also may result from this excessive stimulation. The so-called "neurasthenia" so commonly found in cases of neglected ptosis of the kidney is undoubtedly caused by excessive stimulation of the sympathetic nerves.

3. The sagging of the midportion of the duodenum can be demonstrated easily by fluoroscopic examination of the gastro-intestinal tract, particularly if this is made with the patient standing and in conjunction with retrograde pyelography.

4. The frequency with which ureteral kinks are demonstrated in cases of ptosis of the kidney is probably quite misleading. It is felt that these kinks are not of any particular clinical importance unless there is evidence of renal stasis or of chronic infection of the renal pelvis.

Two types of altered renal mobility are recognized: the asymptomatic and the symptomatic. The latter type comprised at least 60 per cent of all the authors' cases. They have chosen as a basis for discussion a classification of the latter group based entirely on symptomatology, although the extent of alteration in mobility in each of these groups is rather constant.

The cases are classed in four groups: Those in group 1 are characterized by attacks of acute excruciating pain, simulating renal colic, and the other symptoms of renal ptosis are seldom present. This type of pain is found almost as frequently on the left as on the right side. Often the patient can date the onset of his symptoms from the time of some unusual physical exertion or an accident. The cases in group 2 are characterized by marked gastro-intestinal symptoms suggesting pyloric or duodenal obstruction. Occasionally these are so severe that they have been the cause of a previous operation, such as appendectomy or cholecystectomy. Those in group 3 are characterized by occasional attacks of rather severe renal colic and a marked tendency toward a recurrent pyelitis and hematuria. Symptoms of chronic dyspepsia are usually present. There is in these cases a definite tendency toward neurasthenia. Examination reveals the kidney to have a movement of from 1½ to 3 inches (3.57 to 7.6 cm.) and frequently gives evidence of urinary stasis. It is in this group, which comprised 48 per cent of their series, that the authors had the most uniformly satisfactory results. The cases in group 4 are characterized by more or less constant heaviness and dragging in the side, and usually symptoms suggestive of chronic renal infection are present. If these symptoms are on the right side, symptoms of mild, chronic dyspepsia are usually present also. Examination reveals a very low-lying kidney and usually a dilated and infected renal pelvis.

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[6] Smith, P. G.: McKim, G. F., and Rush, T. W.: Nephropexy for Disabilities Due to Abnormal Renal Mobility, Ann. Surg. **103**:924-934 (June) 1936.

The vast majority of unsatisfactory postoperative results are attributable to one or more of the following causes: (1) failure to restore the kidney to its proper position, (2) production of excessive trauma about the renal pedicle or the ureter at the time of operation and (3) failure to recognize coexistent pathologic changes in the kidney or adjacent organs.

Calculi.—Marion[7] stated that after the successful removal of renal, pyelic or ureteral stones the general condition of the upper portion of the urinary tract in some cases is disappointing, as the patient frequently continues to suffer from urinary disturbances. In some cases an existent infection continues, or the kidney performs its excretory duties poorly; pockets may exist which have become cicatrized, and in the course of a few years pyonephrosis supervenes. Another tendency of kidneys that have been calculous is toward sclerosis. The kidney atrophies and becomes deformed; and the calices and pelves take on atypical characters, notwithstanding the fact that no fresh calculi have formed.

In some cases in which a ureteral calculus has been removed in the expectation that the patient would be relieved of urinary troubles, relief has failed to materialize, and, instead, the ureter has become cicatrized and its canal totally obliterated. This obliteration progresses silently and results in considerable atrophy of the kidney on the same side. Several cases were cited to illustrate these various pathologic changes. In some cases in which it might have been possible to reconstruct a working ureter, the function of the kidney continued to be deficient. In other cases so much periureteritis was present that the continuity of the ureter could not be restored, and the patient must carry a urinary fistula all his life because of changes in the ureter and the kidney.

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[7] Marion, G.: De l'évolution des reins après l'ablation des calculs du rein, du bassinet où de l'uretère, J. d'urol. **42**:193-204 (Sept.) 1936.

From all these cases Marion concluded that the prognosis in operations for suppression of reno-ureteral calculi must be reserved, since without reappearance of calculi lesions may be established as the result of sclerosis, which finally lead to destruction of an organ which it had been hoped could be saved by removing the cause of the primary infection.

[COMPILERS' NOTE.—It should be borne in mind that the removal of calculi from the upper portion of the urinary tract is only the beginning of the necessary treatment. It is essential after removal of the stones to institute measures to secure good drainage and to relieve the infection. These two desiderata can be readily obtained by nephrostomy followed by routine cystoscopic treatments with dilations of the ureters and lavage of the renal pelvis. These treatments should be carried out at first once a week, then once in two or three weeks and later once a month; it may even be necessary to repeat them once or twice a year for a long period. Finally, the urologic condition of the patient should be checked occasionally for a reasonable length of time by intravenous urograms, and sometimes a special dietary regimen also should be instituted.

When such control is not properly maintained, we must agree with Marion that the outcome of surgical intervention for relief of nephroureterolithiasis is very poor, particularly in clinic cases in which the condition is beyond control. But when the fundamental principles of drainage, relief of infection and administration of a proper diet are carried out under the systematic control of a follow-up clinic, the results are gratifying.]

Priestley and Osterberg[8] briefly discussed the current theories of the etiologic factor of renal calculi, namely, stasis, infection, vitamin deficiency, other dietetic errors, metabolic disorders, endocrine disturbances, abnormalities of the p_H of the urine, various alterations of the urinary colloid-crystalloid relationship, local ulcerating lesions in the collecting portion of the kidney, etc. It seems unlikely that the etiologic factor is the same in all types of calculi. For example, cystine, urate and phosphate stones are obviously formed by a different process.

The authors studied 193 cases in which stones composed chiefly of calcium oxalate, of calcium phosphate associated with varying amounts of calcium carbonate or of urates were removed from the urinary tract. In each case the chemical composition of the stone was determined.

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[8] Priestley, J. T., and Osterberg, A. E.: The Relationship Between the Chemical Composition of Renal Calculi and Associated Bacteria, J. Urol. **36**:447-459 (Oct.) 1936.

and in many cases the preoperative p_H of the urine was determined and cultures of the urine and calculi were made. Cystine, xanthine and other uncommon types of stones were not included in the study because the data on these calculi seemed insufficient to be significant. There were 93 oxalate stones, 71 phosphate stones and 29 urate stones.

It was noted that calculi of different chemical composition are not found with equal frequency in all parts of the urinary tract. For example, 82.8 per cent of the oxalate stones were removed from the kidney or ureter, and, in contrast, only 48.3 per cent of urate stones were removed from the upper part of the urinary tract. Approximately 62 per cent of the phosphate calculi were removed from the kidney or ureter, and the remainder were removed from the bladder. Apparently urate and phosphate stones form somewhat more frequently in the bladder than do oxalate calculi. It seems possible that the site of origin of a calculus may be of etiologic significance. It was found that approximately 25 per cent of the phosphate and urate stones were bilateral, whereas only 13 per cent of the oxalate stones were bilateral. The average incidence of bilateral calculi in cases of nephrolithiasis is approximately 15 per cent. Recurrent stones are more often composed of phosphates than of oxalates. The rapidly reforming stone is almost invariably of phosphatic origin, although the original calculus may have been of a different nature. In this regard it is mentioned that phosphates normally occur in the urine in much larger amounts than do urates or oxalates.

All types of renal calculi may be associated with infection; however, in some cases infection is apparently present prior to precipitation of the stones, and in other instances it is a secondary development. Phosphate stones were found associated with bacteria in the urine in approximately 59 per cent of cases, whereas oxalate stones were found in infected urine in only 28 per cent and urate stones in 21 per cent of cases. Cultures of the stones themselves usually correspond closely to the cultures of the urine, although this is not always true. Many different types of bacteria are found associated with calculi, Escherichia coli being found most frequently. The relatively high incidence of Proteus ammoniae in association with phosphate stones is emphasized. Multiple types of bacteria were found more often in the presence of phosphate stones than they were with any other type of calculus. The wide variety of organisms that may be present indicates that under proper circumstances many different types of bacteria may be associated with the precipitation of stone.

The importance of p_H of the urine in the etiology of lithiasis was considered. Although the exact chemical sequelae of variations in p_H are not clearly understood, the resultant changes in solubility, colloidal protection against precipitation of crystalline material, ionic equilibrium and other factors may have an important influence on the formation of stones. The p_H of the urine was invariably higher when infection was present. Normally, phosphate stones are associated with the highest p_H, oxalate stones with a somewhat lower p_H and urate stones with the lowest p_H of all.

Barney and Mintz[9] stated that although hyperparathyroidism is responsible for between 4 and 5 per cent of all cases of urinary stone, in almost 70 per cent of the cases of this disease stones may be present. It is also true that in about 38 per cent of cases of hyperparathyroidism patients may have pathologic changes in both the bones and the urinary tract. This disease does not seem to be a factor in the production of bilateral urinary lithiasis. The symptoms and signs of urinary lithiasis in cases of tumor of the parathyroid glands do not differ from those attributable to other causes. After removal of the tumor stones do not recur. Barney and Mintz expressed the belief that today no physical examination is complete without a careful study of the calcium and phosphorus content of the blood, especially if urinary lithiasis is present or is suspected.

Higgins[10] stated that diet is of definite benefit to the following groups of patients and that the best results are secured among such patients:

In the first group are the patients in whom there is a tendency to the recurrent formation of calculi after operation. A review of the cases at the Cleveland Clinic up to 1932 revealed recurrence in 16.4 per cent, but since a special diet has been prescribed as a routine after operation, this has been reduced to 4.7 per cent. Higgins stated that it may be too early to report these figures, for two years is the maximal period since operation, but he definitely expressed the opinion that a dietary regimen should be included in the postoperative care in addition to the therapeutic procedures employed previously. By following this principle, the cause and not the effect alone of the disease is treated.

In the second group of patients are those who have passed stones at frequent intervals but in whom larger calculi cannot be demonstrated in the kidney. At the Cleveland Clinic 40 of the patients in this group have been free from symptoms for two years.

The third group consists of orthopedic patients in whom stones develop while they are in the hospital. As a general rule, the stones are composed of calcium and magnesium phosphate, namely, stones which form in an alkaline urine. If the high vitamin A acid ash diet is prescribed for these patients while they are forced to remain in a recumbent position, thus shifting the reaction of the urine to the acid side, the chemical possibility of the development of such calculi is reduced to a minimum.

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[9] Barney, J. D., and Mintz, E. R.: The Relation of the Parathyroid Glands to Urinary Lithiasis, J. Urol. **36**:159-167 (Aug.) 1936.

[10] Higgins, C. C.: Urinary Lithiasis: Experimental Production and Solution with Clinical Application and End-Results, J. Urol. **36**:168-177 (Aug.) 1936.

Higgins seemed to be quite certain that if the patients who live in those communities in the United States which have been reported as stone areas could receive adequate amounts of vitamin A, the formation of calculi could be prevented in a large percentage.

It is difficult to say when stones will undergo dissolution. In one case a stone had not changed in size for eleven months until an attack of colic occurred recently. The stone was situated in the lower calix of the kidney, and some days after the attack of colic a considerable amount of sand was passed, and the large stone disappeared. On the other hand, in many cases response is not secured; the reason for this is not known. In an effort to explain this, Higgins is studying the outer coating of the stones and making a more careful quantitative analysis of them. After operation the renal pelvis is lavaged with 1 per cent solution of phosphoric acid, as suggested by Randall.

Higgins has studied a series of more than 35 cases in which complete urologic examination revealed renal calculi. These stones have been caused to undergo complete dissolution and have disappeared after the patient had followed the prescribed dietetic regimen.

In view of the fact that patients who have a duodenal ulcer and who are treated by the Sippy routine are given considerable amounts of alkali and as a general rule have a strongly alkaline reaction of the urine, Higgins expressed the belief that cod liver oil or halibut liver oil should be prescribed as a routine. He emphasized this because many cases have been reported in which calculi developed or were passed while the patients were being treated by this method.

Higgins,[11] in discussing prevention of recurrent renal calculi, stated that recurrent calculus formation occurs with sufficient frequency to be a seriously complicating factor in the surgical treatment of nephrolithiasis. Empirical treatment which has been employed in the past does not reduce the percentage of recurrence below 10 or 15. The alkaline or acid ash diet with a high vitamin A content should be prescribed after operation, the constituents of which depend on the p_H of the urine and the chemical constituents of the calculus. A group of 31 patients who previously had had frequent attacks of renal colic and had expelled small stones spontaneously have been free from symptoms for more than two years on dietary management. During the past four years, since this diet has been used in conjunction with other therapeutic agents, renal calculi have recurred in 4.7 per cent of the cases studied. This percentage, which is higher than was anticipated, was believed to be attributable to the fact that roentgen examination was not performed as a routine after operation and, thus, that some of the recurrences may have been false in type.

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[11] Higgins, C. C.: Prevention of Recurrent Renal Calculi, Surg., Gynec. & Obst. **63**:23-34 (July) 1936.

Hydronephrosis.—Campbell[12] reported a case of hydronephrotic renal destruction secondary to a ball-valve papilloma at the pelvic outlet. Chief interest focuses on the diagnosis; attention is directed to the urographic filling defect caused by the growth but which might justifiably be thought to be produced by a nonradiopaque calculus. Nephrectomy is the usual treatment.

Ormond[13] reported 6 unsuccessful operations for hydronephrosis, 5 of which were for obstruction at the ureteropelvic juncture. Of the latter, 2 were converted into apparent successes by second operations. Experiences such as these do not warrant dogmatic or authoritative statements. Ormond stated that in view of this experience and in view of the results reported in the literature he was justified in drawing the following tentative conclusions:

> The Heineke-Mikulicz type of operation should be distrusted in the future. It seems to be best suited to cases in the early stage in which there is no infection, and in many such cases reimplantation of the ureter has given satisfactory results. Ureteropyeloplasty has no advantages over reimplantation. It is rather difficult to perform with precision, for the kidney and the ureter are drawn up out of their natural positions in order to obtain exposure, and the line of incision and repair might be distorted when the organs are restored to their normal positions.
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> Resection of the ureteropelvic juncture should be favored, and the ureter should be cut on a slight bias to lessen the likelihood of stricture from contraction of the suture line and reimplanted into the lowest portion of the pelvis, with accurate apposition of the cut edges. The ureter should not be allowed to protrude into the pelvis at all. This is not difficult, and with a catheter running through the cortex and pelvis of the kidney and down the ureter, the first sutures nearly always can be made as the ureter and pelvis lie in situ. In every case a splinting catheter should be used, there being no haste about removal. In the

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[12] Campbell, M. F.: Hydronephrosis Due to Ball-Valve Obstruction by Papilloma at Ureteropelvic Junction, Am. J. Surg. **33**:291-293 (Aug.) 1936.

[13] Ormond, J. K.: Unsuccessful Plastic Operations for Hydronephrosis, J. Urol. **36**:512-528 (Nov.) 1936.

presence of acute, or marked, infection, preliminary nephrostomy should be performed. In every case in which the kidney is not bound down by adhesions, preventing mobility, nephropexy should be performed.

Plastic operation should be reserved for those cases in which conservation of renal function is imperative or for those cases in which the desirability of conservation of renal function outweighs the chance of increased expense, danger and loss of time.

Campbell[14] stated that vascular compression of the ureter is not uncommon in children. Vessels which produce the obstruction are congenitally anomalous. Hydronephrosis is the important uropathy, and infection usually is present. The commonest symptoms are pain in the renal region, pyuria, hematuria, a mass in the loin and, after the advent of infection, fever. Most children with vascular obstruction of the ureter are treated for months for chronic pyelitis. In the absence of infection, the renal changes, as interpreted by urinalysis, are regularly diagnosed as those of chronic interstitial nephritis. Yet the correct diagnosis usually can be made preoperatively by a complete urologic examination. The correct diagnosis is often suggested by the excretory urogram. Delayed diagnosis and radical surgical treatment are usually reciprocal. Nonoperative treatment has no place. Conservative surgical treatment may be expected to save a gratifying number of injured kidneys. Unfortunately the medical profession is as yet insufficiently alert to the high incidence and importance of urologic disease in children. Because of the consequent delay in making the diagnosis, nephrectomy will necessarily be the treatment for fully half of the children with vascular ureteral blockage.

Renal Abscess.—Emmett and Priestley[15] reported a case of solitary renal abscess. The original roentgenogram of the urinary tract revealed a large shadow of a soft tissue mass in the left side of the abdomen. The shadow of the psoas muscle on the left side was much less distinct than that on the right. An intravenous urogram revealed a normal right kidney. The pelvis of the left kidney, which was approximately normal in size, was flattened on its lateral aspect by a soft tissue mass situated in the region of the lower pole of the kidney. The calices were elongated and distorted. The upper calix was flaring at its tip, and the middle calix was flattened against the pelvis. The lower calix was only partially visualized, and obliteration of its lower part was suggested.

At operation the upper half of the kidney appeared to be normal, but in the lower pole there was a large inflammatory mass which was densely adherent to the peritoneum and adjacent structures. During mobilization of the lower pole, some nonodorous pus was encountered. Nephrectomy was performed. The tissues, including the peritoneum, which had surrounded the lower pole, were indurated, inflamed and thickened. This region was packed with iodoform gauze, and the wound was closed loosely with a few interrupted sutures. In the lower pole of the kidney there was a large, well circumscribed abscess, with multiple points of discharge typical of the so-called renal carbuncle.

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[14] Campbell, M. F.: Vascular Obstruction of the Ureter in Children, J. Urol. **36**:366-387 (Oct.) 1936.

[15] Emmett, J. L., and Priestley, J. T.: Solitary Renal Abscess (Carbuncle): Report of Case, Proc. Staff Meet., Mayo Clin. **11**:764-767 (Nov. 25) 1936.

In contrast to the majority of renal lesions, the correct preoperative diagnosis of renal carbuncle is usually difficult to make, primarily because no characteristic deformity is revealed in the urogram. If the lesion is small, the outline of the pelvis and calices may be perfectly normal; if it is large enough to produce deformity, this deformity frequently simulates that of a neoplasm or cyst. In the roentgenogram diminution in intensity or absence of the shadow of the psoas muscle on the affected side, associated with scoliosis of the spinal column, may call attention to the condition, especially if considerable perinephritis is present.

Carbuncle of the kidney, like a smaller unilocular cortical abscess, is considered a manifestation of a blood-borne infection. It usually develops slowly over a period of some weeks or months, during which interval there is a paucity of symptoms. Depending on the duration and extent of the process, perirenal involvement will be slight or extensive. Treatment is surgical and consists of either resection of the carbuncle or nephrectomy. Removal of the kidney is usually advisable if the other kidney is normal, as conservative procedures are often followed by prolonged convalescence and nephrectomy may be necessary in the end.

Tuberculosis.—Mazzarelli[16] carried out experiments consisting of the inoculation of tubercle bacilli into the perihilar tissue of the kidney and into the wall of the ureter, by which he was able to produce tuberculosis of the renal pelvis and the corresponding renal parenchyma.

In the majority of the experiments inoculation was followed by generalized tuberculosis, which included also a renal localization. The tubercle bacilli evidently came to the kidney by way of the blood stream. In some cases, however, the tuberculous changes were strictly confined to the zone of inoculation, that is, to the corresponding kidney and the regional lymph glands, without any localization in other organs; in these instances diffusion to the kidney by way of the blood stream must be excluded, and diffusion by the lymphatics must be assumed. These cases were relatively rare, but they prove that this mode of infection of the kidney is a possibility. Infection by this route has been admitted in cases of pulmonary localization, and there is no reason why it should not be possible for other organs as well. All authors agree that tuberculosis of the kidney is practically always secondary, although Albarran collected from the literature reports of 6 cases of primary renal tuberculosis. After an extensive review of the literature, Mazzarelli pointed out that ascending infection was once believed to be the common route for renal tuberculosis, Albarran himself being among those who held this view. Today, however, it is believed that this is the route only under favorable conditions, such as exist when the sphincter of the ureteral meatus is weak or absent, so that vesicorenal reflux occurs.

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[16] Mazzarelli, M.: Considerazioni e ricerche sulla patogenesi della tubercolosi renale, Arch. ital. di urol. **13:**119-166 (March) 1936.

The deep and superficial lymphatics of the kidney and also those of the fatty capsule empty into the corresponding para-aortic lymph nodes, which thus become the regional lymph nodes of the kidney. But these may also receive lymph from other abdominal and pelvic organs, such as the hilus of the kidney, the ureter, bladder, urethra, prostate gland, seminal vesicles and testes; all of these lymphatics were traced by the author. Between all of these lymph channels there are anastomoses, and any of them may flow into the same abdomino-aortic ganglions. In the lymphatic infection of the kidney three routes were distinguished: (1) the ascending ureteral route, (2) the retrograde route and (3) the route from nearby organs. Experiments were done to discover whether renal tuberculosis could be produced by the lymphatic route, through infection of the ureteral walls or the tissues about the pelvis or hilus, whether an inflammation of the testis could be started by the lymphatic route and, finally, the modes by which this infection is developed. The author found that he could produce specific changes which often remained localized at the point of inoculation or in nearby zones but were sometimes diffused. Thus, after one hundred and eighty days he found tuberculosis localized exclusively to the kidney or ureter in 4 of 25 experiments, which gives a relatively high percentage. In the other experiments there was most often a generalized tuberculosis, with concomitant renal lesions, which had developed because of injection by the hematogenous route, and therefore these were not counted. Apparently the bacilli are diffused along the submucous spaces, where there is a rich lymphatic network, and in cases of lymphatic infection they are carried upward by the lymphatic current to the renal pelvis.

Sutherland and Braasch[17] reviewed the development of the roentgen ray and its use in urologic diagnosis. Important anatomic characteristics of the kidney were emphasized in their relation to the roentgenographic diagnosis of tuberculosis. The pathologic changes caused by early tuberculosis in the kidney were considered. A review was made of 1,314 cases in which the patients were treated surgically and the presence of renal tuberculosis was proved by microscopic examination. In 1,157 of these cases a preliminary plain roentgenogram of the genito-urinary tract was made, and in 237 cases (20.6 per cent) the findings were positive; that is, some abnormality was present which suggested the presence of a lesion in the genito-urinary tract. These abnormal findings included alteration in the size and contour of the soft tissue shadow of the kidney; more or less extensive calcification in the region of the kidney, which was occasionally misinterpreted as evidence of renal calculi; indeterminate types of shadow, and calcified lymph nodes. In the roentgenogram the margin of a tuberculous calcified area is usually rough and irregular, whereas that of a calculus tends to be more discrete and smooth in outline. Shadows of tuberculous calcifications are found more frequently in the region of the cortex, whereas those of calculi are commonly seen in the pelvis or in the calices. There is frequently a difference in the intensity of the shadow cast by a tuberculous lesion in contrast to that cast by a renal calculus. As mentioned previously, there was some evidence of abnormality in the plain roentgenogram in approximately a fifth of all cases. Retrograde and excretory urography were then employed in order to establish a definite diagnosis. At times excretory urography alone gives sufficient information on which to base diagnosis and treatment. Frequently, however, cystoscopy and retrograde pyelography are essential.

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[17] Sutherland, C. G., and Braasch, W. F.: The Value of Roentgen Rays in the Diagnosis of Renal Tuberculosis, Tubercle **17**:*309-317* (April) *1936*.

It is the consensus that renal tuberculosis is never a primary condition. In this series roentgenographic examination of the thorax was made in 911 cases. In 280 cases (30.7 per cent) there was evidence of pulmonary tuberculosis, which in the majority of cases was latent. In 83 of 1,314 cases tuberculous lesions were coexistent in bone. Fortunately, at present patients consult the physician earlier than they did formerly. Today renal tuberculosis is suspected when dysuria persists over a period of one or two months; the urine is stained for tubercle bacilli, and in cases in which the diagnosis is doubtful guinea-pigs are inoculated, cystoscopic examinations are made, the kidneys are catheterized and pyelograms are made. Renal tuberculosis in the advanced stage with severe ulceration and deformity of the bladder is encountered less commonly. It is generally believed that the condition is hematogenous and begins in the kidney rather than in the bladder. The infecting agent passes through the capillary system of the glomeruli and settles in some portion of the collecting system. Then, by a retrograde process, it passes up the lymphatic structures and infects the cortex. The lesion is probably unilateral in the beginning and may remain so for a remarkably long time. The incidence of primary bilateral renal tuberculosis, on the other hand, is probably greater than was previously supposed; the possibility of spontaneous recovery in the early miliary type of renal tuberculosis must be recognized. The importance of preoperative and postoperative hygienic treatment in assuring the best prognosis cannot be overemphasized.

Definite limitations and possibilities of error in the use of the excretory urogram as a single method of diagnosis in cases of renal tuberculosis are mentioned. In the differential diagnosis the changes resulting from pyogenic pyelonephritis are most frequently confused with those of tuberculosis. In the urogram deformity occurring with pyelonephritis tends to be more commonly uniform; all of the calices are likely to be involved by inflammatory dilatation, and evidence of cortical involvement is much less frequent. In the retrograde urogram artefacts from overdistention or incomplete distention may simulate tuberculosis, and extravasation may cause shadows in the parenchyma distal to the tips of the minor calices which may be confused with those of cortical necrosis as a result of tuberculosis. Likewise, nephrolithiasis, when associated with pyelonephritis or pyonephrosis and cortical abscesses, may simulate tuberculosis closely in its urographic manifestations. Tuberculosis may invade the perinephric tissues, and the outstanding roentgenographic evidence will be obliteration of the shadow of the psoas muscle on the affected side. Carcinoma of the kidney not infrequently is attended by calcification in the primary tumor, and such calcification may be mistaken for tuberculosis. Likewise, necrosis may be caused by malignant involvement. Roentgenography does not play an important part in the identification of tuberculosis in the genital organs.

Weber[18] found that in nearly all instances the end of the ureter which had been sewed into the skin after nephrectomy for tuberculosis contained tubercle bacilli on culture on the second and third postoperative days. He considered this as a proof that the stump of the ureter is often the source of a fistula. In his cases the formation of a fistula postoperatively was much rarer when the ureter was cut after the renal pedicle was clamped and then tied and brought out to the skin. He recommended this as a standard procedure in nephrectomy for tuberculosis.

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18. Weber, Herbert: Zur Vermeidung postoperativer Fisteln bei Nierentuberkulose (Tuberkelbacillenkulturen aus dem Ureterstumpf), Ztschr. f. urol. Chir. u. Gynäk. **42**:416-428 (Dec.) 1936.

Pelz [19] stated that the microscopic examination of a stained smear of the urinary sediment in cases of renal tuberculosis often gave negative results. Results of inoculation of guinea-pigs are usually positive, but the method necessitates waiting too long. The culture method of Löwenstein gave positive results in 88 per cent of cases of renal tuberculosis and in 55 per cent of the cases of tuberculous epididymitis. Fifty-five patients were examined. It is interesting to note that sometimes cultures of blood were positive for tuberculosis at an earlier time than the cultures of the urine.

Hemorrhagic Cysts.—Barney [20] reported 2 cases of hemorrhagic cyst of the kidney. The hemorrhage in case 1 was acute and gave rise to a train of obscure subjective and objective symptoms. The etiology was unknown, but the possibility of infection or trauma and perhaps embolism or thrombosis should be considered. The presence of another cyst in the same kidney, which was thin walled and filled with serous fluid, increased the probability that what ended as a hemorrhagic cyst might well have started as a serous cyst.

In case 2 nothing was known of the antecedents of the condition. The fact that the kidney opposite to the one which contained the hemorrhagic cyst contained three serous cysts might allow one to follow the same train of thought as in case 1. On the other hand, the calcified wall surrounding the blood clot would indicate an ancient process, with symptoms so insignificant that the patient did not notice them.

In case 1 there were no symptoms, subjective or objective, previous to the onset of the hemorrhage. At this time the symptoms were very suggestive of renal colic, caused perhaps by calculus. There was in addition a strong suggestion of a rather severe but obscure hemorrhage. The pain and tenderness can be accounted for by the sudden increase of tension within the cavity of the cyst.

In case 2 there were evidently no signs or symptoms during life which could be elicited by the history or physical examination. The calcified wall of the cyst is indicative of a long-standing process, and the hemorrhage into it was not extensive enough to have caused symptoms at the time it occurred.

These 2 cases illustrate that cysts of the kidney may, and in fact often do, exist for an indefinite and probably a long time without giving rise to symptoms. The factors which bring about their recognition are pressure, pain, the presence of a tumor, intracystic pressure and acute hemorrhage.

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[19] Pelz, S.: Nachweis der Tuberkelbazillen bei Urogenitalerkrankungen durch das Kulturverfahren nach Professor Löwenstein, Wien. med. Wchnschr. **86**:1027-1029 (Sept. 5) 1936.

[20] Barney, J. D.: Hemorrhagic Cyst of the Kidney, J. Urol. **36**:602-608 (Dec.) 1936.

Hydatid Disease.—Begg[21] stated that a total of approximately 800 cases of hydatid disease of the kidney is available for study. The incidence of the disease fluctuates in a given country with the number of sheep, the living conditions, the level of culture and the efficacy of preventive measures.

Renal cysts may be classed according to their relation to the renal pelvis as open, closed and pseudoclosed. In the first type both the pericystic and the endocystic cavity communicate with the pelvis; in the second type neither cavity communicates with the pelvis, and in the third type, only the pericystic cavity, the ectocyst remaining unruptured. Symptoms are characteristic for each type of cyst. In the open cyst they consist of renal colic and the passage of hydatid elements in the urine; in the closed cyst the symptoms are usually attributable to pressure; in the pseudoclosed cyst the typical manifestations are intermittent attacks of pain localized to the loin due to colicky pain of the calix and perhaps urinary symptoms, such as hematuria or frequency, but no hydatid material is passed.

The etiology of hydatid disease of the kidney is that of hydatid disease in general. The industry of sheep raising, on the one hand, and insanitary conditions of life, on the other, contribute chiefly to its incidence and spread.

Unlike the liver, the kidney is almost invariably the site of one primary cyst only. In the larger series of cases the incidence of involvement of each kidney is equal, and bilateral cysts are rare. Nicaise found involvement of the right kidney in 197 cases, of the left kidney in 185 cases and of both kidneys in 12 cases. The sexes are equally vulnerable. Most patients are infected in childhood, and the third to the fifth decade is the commonest period for the development of symptoms. In the reported cases the youngest patient operated on was a child aged 2 years. The commonest site of the cyst is the cortex of the anterior surface at the upper and lower poles.

In the kidney, as elsewhere, the hydatid cyst develops slowly, though growth may be stimulated by trauma or pregnancy. Expansion is centrifugal, but the center point of the sphere is not static. As a rule the line of least resistance is followed, but in an effort to preserve its circular contour the cyst may burrow into the spleen, into the liver or into the tail of the pancreas. The hydatid may die of old age or lack of nutriment. There is a ring of large blood vessels in the pericyst, a striking feature microscopically. Thus ample serum is brought to the hyaline laminated membrane, from which the parasite can select its food supplies. Calcification hinders the osmotic process. The animal feels the urge for more defensive propagation. Daughter cysts are born in large numbers and even granddaughter cysts. Tension may become low, and growth may be in abeyance or spasmodic. The whole tribe may perish and be buried in lime, or sepsis may supervene. Low grade life may, however, be maintained, even though the pericyst is heavily calcified.

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[21] Begg, R. C.: Hydatid Disease of the Kidney, Brit. J. Surg. **24**:18-40 (July) 1936.

The expanding pericyst may become incorporated in the stomach, spleen, pancreas, colon, liver, duodenum or vena cava. The adrenal glands may become inseparably fused. Such a welding of tissues becomes a danger at operation, chiefly if the surgeon confuses it with an ordinary adhesion and attempts to separate the inseparable. There is no reason why a large cyst at the upper pole should not rupture into the bronchial system. Complications within the urinary tract include hydronephrosis, pyonephrosis, lowering of capacity of the kidney on both sides from difficulty in micturition or chronic retention from an accumulation of membrane in the bladder, with or without bilateral ascending pyelonephritis. All are rare and usually are attributable to sepsis. The ureter on the affected side may become completely occluded.

Calculus associated with hydatid cyst is rare, even in such countries as Dalmatia, in which both conditions are common.

Symptoms may not appear for many years, and the patient may be ignorant of the existence of the cyst till the day of his death. A closed cyst may be found accidentally in a person who is perfectly well. The parasite may produce unexplained anaphylactic phenomena, such as urticaria or symptoms of obscure pressure. A closed cyst that grows toward the abdomen causes indigestion, pain and fulness after meals by encroaching on the stomach, or diarrhea, constipation or even complete obstruction by pressure on the colon.

In the case of an open cyst diagnosis is made from examination of the material passed. If this is only hydatid sand or brood capsules, the condition may be considered as merely caused by the passage of gravel, and the patient may have to wait some time before a microscopic examination of the sediment discloses hooklets and scolices. A calcified cyst may produce solid débris, which when passed is mistaken for calculus. A pseudoclosed cyst is demonstrated by a typical pyelogram. A closed cyst is most difficult to demonstrate. Clinically, it appears as a tumor of the hypochondrium or as a free and mobile tumor of the abdominal cavity. If the muscles are rigid, such a tumor may be missed during an attack of renal colic. The commonest error in diagnosing a tumor in the hypochondrium is to mistake a cyst on the left side for an enlarged spleen, especially in communities in which malaria is endemic, or one on the right side for a cyst of the liver. In the case of the former the special serum tests, with roentgen examination and pyelograms, usually clear up the diagnosis; in the case of the latter, serum tests are useless. A cyst at the upper pole of the kidney may produce a high area of dulness at the base of the lung of the corresponding side and has to be distinguished from an intrathoracic condition or a splenic cyst as well as from hydronephrosis. The greatest calamity in such cases is a diagnostic puncture. When there are no physical signs, routine urologic examination may reveal deformity of the renal pelvis, and the serum tests may eliminate other confusing renal conditions.

Roentgenographic examination may reveal a density due to the high saline content of hydatid fluid or a typical curvilinear shadow of a calcified pericyst. In all types of cases complete urologic investigation usually gives fairly conclusive information.

The precipitin test is rarely used. The complement fixation test, worked out by several persons, is a laboratory procedure requiring rigid conditions of technic to give its best results. The intradermal reaction of Casoni, taking into account both the immediate and the delayed reaction, is simple, practical and of great value.

From the statistics available, hydatid disease of the kidney appears on the whole to be relatively innocuous. Of the 474 cases of Nicaise, 20 per cent were found in the course of routine postmortem examination; 215 of the patients received no surgical treatment, and only 16 died as the direct or indirect result of the cyst. The first attack of colic and the passage of membrane may be the last in spite of an active parasite. Impairment of renal function to a dangerous level is rare even in cases of long standing, and the general health of the patient is seldom affected. Spontaneous cure occurs in many cases, though symptomatic cure is probably more common than anatomic.

Treatment is mainly surgical or expectant. Turpentine has been used to assist elimination of the daughter cysts. No intravenous therapy is effective. Nephrectomy was introduced by Bockel in 1887 to replace the universal method of marsupialization. Intervention must be governed by two considerations: In the first place the disease is benign, and a cyst once communicating with the pelvis as a rule ceases to grow because the level of tension required in the fluid for this purpose reopens the safety-valve. In the second place radical operation is difficult because of the dense adhesions and is not to be undertaken lightly.

As a rule operation is not indicated in the following circumstances: 1. After a first attack in which cysts are passed in the urine when investigation reveals that only a small cyst is present and that renal function is good on both sides. The danger of complications is small, and subsequent intervention may be undertaken if disabling symptoms or septic complications occur. 2. If the other kidney is absent, infantile or functioning badly from any cause and no serious disability is caused by the hydatid. In the best hands any difficult operation on a kidney may lead to damage demanding nephrectomy, and the risk of operation is greater than that of the parasite. 3. If the cyst is calcified and dead, unless passage of the calcified fragments threatens damage to the urinary tract or is seriously disabling.

In most other cases nephrectomy, if possible, is the operation of choice if the other kidney is normal in function, for the following reasons: 1. The mortality is low, convalescence is short and health is quickly restored. 2. Secondary cysts may exist in the calix, making recurrence inevitable if the kidney is left. These cannot be detected during any conservative operation. 3. An apparently closed cyst may really be of the pseudoclosed type, and with conservative operations there is danger not only of recurrence but of infecting the urinary tract. 4. In many cases the whole of the pericyst cannot be removed, and in these instances recurrence is common. If the kidney is left, the old symptoms of renal colic and the passage of membrane will recur. When the kidney is removed, the recurring cyst will cause no trouble and in the course of many years will reach the surface in the loin, where it can be easily dealt with.

Circulation.—Anson, Richardson and Minear[22] studied the variations in the number and arrangement of the renal vessels of 400 kidneys. In only 35 per cent of 200 consecutively examined cadavers were the renal arteries of both sides arranged in the simplest pattern, namely, with a single vessel supplying each kidney. In 65 per cent of the 200 cadavers a unilateral or a bilateral anomaly of the renal arteries was present, a condition so regularly prevailing that it certainly should no longer be regarded as anomalous. In 20 per cent of the bodies the simple arrangement of renal vessels occurred on the right side, accompanied by supernumerary arteries on the left side; in 17 per cent, a single vessel supplied the left kidney and multiple vessels the right; in 28 per cent, multiple vessels supplied the right kidney, and in 28 per cent, multiple vessels supplied both kidneys. Of the 400 kidneys, 53 per cent were found to have a so-called normal arterial supply. The remaining 47 per cent possessed extra-arterial branches.

The authors encountered no kidney in which the number of supernumerary vessels exceeded four (three from the aorta to the hilus and one from the renal artery to the extremity). From the data obtained on the renal tributaries of the inferior vena cava in the same group of 400 kidneys, it is strikingly evident that venous variations are relatively few.

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[22] Anson, B. J.; Richardson, G. A., and Minear, W. L.: Variations in the Number and Arrangement of the Renal Vessels: A Study of the Blood Supply of Four Hundred Kidneys, J. Urol. **36**:211-219 (Sept.) 1936.

Hyman[23] made a study of 6 cases of suppurative disease of the kidney complicated in 5 instances by suppurative thrombophlebitis of the renal vein; the diagnosis was confirmed by operation or postmortem examination. Since this condition is nearly always secondary to a suppurative lesion in the kidney, the diagnostic criteria are not sufficiently clearcut to differentiate thrombophlebitis from the primary disease of the kidney, which in 5 cases was a cortical abscess. The clinical picture is essentially one of sepsis with or without bacteremia. If sepsis is not controlled after adequate drainage of a suppurative focus in the kidney or after nephrectomy, thrombophlebitis of the renal vein should be suspected. It should be realized that the kidneys are often the seat of localized metastatic abscesses following cutaneous staphylococcic infections. With this type of infection, invasion of the blood stream by staphylococci not infrequently occurs. If after drainage operation and decapsulation of the kidney, the sepsis persists, nephrectomy should be done and the renal vein ligated as close to the vena cava as possible. If the sepsis persists after a primary nephrectomy, the renal vein should be suspected and explored.

Operation disclosed in 2 instances that thrombophlebitis may be present without causing any recognizable gross changes in the vein. This study further disclosed that in 3 instances the thrombotic process at the time of nephrectomy had already extended into the vena cava. One can well realize that under such conditions nephrectomy even with wide ligation of the renal vein might prove futile.

These 5 cases indicate definitely that suppurative lesions of the kidney act as a source of invasion of the blood stream by the production of a secondary thrombophlebitis. The mortality from this condition is unusually high, because in most instances the sepsis is already widespread before the nature of the disease is recognized.

Pain Syndromes.—Keyser[24] has previously advanced the proposition that pain in the upper part of the urinary tract occurs not infrequently when a small, if any, lesion can be demonstrated clinically and that after repeated scrupulous examinations from many points of view other than urologic, one is at a loss to understand the fundamental pathologic process involved. He presented the hypothesis, and some evidence substantiating it from a series of 60 cases, that nodal spasm of neurogenic background can simulate ureteral stricture and that the clinical course of most of his patients warranted the belief that spasm rather than organic stricture was most often the pain-producing mechanism.

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[23] Hyman, Abraham: Acute Suppurative Thrombophlebitis of the Renal Vein, J. Urol. **36**:196-210 (Sept.) 1936.

[24] Keyser, L. D.: Pain Syndromes in the Upper Urinary Tract: Their Mechanisms and Clinical Management, South. M. J. **29**:953-963 (Oct.) 1936.

He stated: "The differentiation of organic ureteral stricture and of localized nodal spasm is of prime importance. However, this is frequently difficult and at times impossible." One may consider the following criteria: The reproduction of pain on the passage of a bulb bougie or the injection of fluid is presumptive evidence that the seat of the trouble has been found. Keyser stated that the production of pain in this manner does not differentiate spasm from stricture. The bulb bougie, even though it should hang consistently at the same site, does not differentiate spasm from stricture, as the hang may be due to either. With the patient under a good high spinal anesthesia, however, one expects spasm to abate and organic stricture still to be resistant. This is usually, but not always, the case.

Repeated urography with some form of serial plate taking is important. In most instances stricture will show persistent dilatation above its site, while spasm will be unaccompanied by such dilatation.

At present Keyser uses a three plate pyelographic method in the following manner:

> . . . the first plate being taken in extreme Trendelenburg, the second and third as quickly as possible in reversed Trendelenburg or the upright position. In this way one obtains a serial bilateral retrograde urogram and acquires information as to the mobility of the kidneys as a whole, as well as to the variations of motor activity of the pelvis and ureter. . . .
>
> After thorough ureteral dilatation with bulbs one would expect stricture to remain open longer than would spasm and to produce consequent relief of symptoms for a greater period of time. This, however, is not consistently true, as many spastic ureters are relieved indefinitely after the simple passing of the ureteral catheter. In the ultimate, absolute differentiation of stricture and spasm can be made only by operative or autopsy exposure of the obstructing site.

In considering the therapy of ureteral stricture and spastic reno-ureteral syndromes, Keyser stated:

> The procedures to be considered are the dilatation of the ureter with bulb bearing bougies or catheters; the temporary splinting of the ureter with indwelling catheters; the surgical procedures, such as nephropexy, plastic operations on constricted areas, the resection of hydronephroses, and denervation operations on the renal pedicle or the ureter. . . .
>
> In treating painful reno-ureteric syndromes, ureteral dilatation with bulbs and the use of the indwelling catheter have been the initial effort. I have in recent years used the indwelling catheter more and more, especially at the beginning. . . .
>
> Dilatation is not practiced with acute or subacute infection. Here, if conservative measures of oral antiseptic therapy fail, the indwelling catheter is tried, and successively larger sizes are placed every four or five days. It is

remarkable how severe infection may clear up and what remarkable restoration of renal function ensues with a well draining ureteral catheter.

The indwelling catheter or dilation with bulb bougies has in Keyser's experience given complete to partial symptomatic relief in from 60 to 80 per cent of a large enough series of cases to warrant conclusions. He expressed the belief that conservative ureteral dilation is a method worthy of trial before operation is undertaken, not necessarily because of a high incidence of organic ureteral stricture, but as a therapeutic attempt to readjust an unbalanced neuromotor dysfunction.

Surgical Procedures.—Weiser [25] stated that if the pleura is opened during the course of an operation on the kidney it should be sutured immediately. He advised postoperative evacuation of the pneumothorax with one of the ordinary apparatus for pneumothorax suction by means of puncture and suction. Weiser had had occasion to carry out this procedure with complete success.

Sympathectomy.—Gibson [26] stated that renal sympathectomy produces no harmful effects on the kidney; it is surgically feasible either alone or in conjunction with other procedures, and in a number of conditions there are either relative or definite indications for its application.

Among the indications for renal sympathectomy is some type of renal sympatheticotonia, namely, spasm, atony, dyskinesia, hyperdynamic motility and adynamia, either alone or in association with definite organic changes, such as small hydronephrosis, nephroptosis, painful chronic nephritis, painful adhesive perinephritis, essential hematuria, certain types of Bright's disease associated with oliguria and anuria, unyielding reflex anuria and possibly certain stone-forming diatheses.

Renal sympathectomy is recommended, in conjunction with other necessary surgical procedures, as an extra precautionary measure to make doubly sure of complete relief in any case of proved renal pain in which careful investigation reveals few or no demonstrable pathologic changes to explain the symptoms adequately. Whether renal sympathectomy is undertaken as the primary object of a surgical attack on the kidney or is merely incidental to other procedures, no great technical difficulties are encountered if the precautions necessary for adequate exposure of the kidney are observed. The main bugbear of the operation is the possibility of injury to the renal vein, which is as thin walled as tissue paper. If one bears in mind that the nerve fibrils are in the fascia immediately surrounding the renal artery and if the vein is avoided meticulously except to retract it away from the scene of action, this hazard is appreciably diminished. Experience has shown that the best strategy is to start mesially and work laterally toward the renal hilus. The fascia surrounding the vessels is pushed away with gauze sponges and smooth thumb forceps until the vessels are exposed, and the nerves which are then seen in bundles about the artery are picked up with a hook and resected with scissors. Gibson has found it easier in most cases to start the dissection anteriorly but to perform the major portion of it from the posterior aspect after retracting the ureter and the pelvis with a hernia tape. The artery is approached easily from the posterior aspect, whereas anteriorly it is covered by the vein. A hook is essential in picking up the nerves lying directly on the artery as well as for drawing out the fascia containing the nerves from between the artery and the vein. Great care must be taken that the point of the hook does not touch the vein. A small blood vessel retractor is useful at times in protecting the vein from injury. The dissection should not be carried too close to the renal parenchyma, because often small vessels are given off at this level which are easily broken, thus obscuring the field of operation with troublesome bleeding.

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[25] Weiser, Arthur: Vorschlag zur Behandlung des bei Nierenoperationen durch Pleuraverletzung entstandenen Pneumothorax, Wien. med. Wchnschr. 86: 1044-1045 (Sept. 5) 1936.

[26] Gibson, T. E.: The Present Status of Renal Sympathectomy, J. Urol. 36: 334-363 (Oct.) 1936.

Oldham, after stripping the pedicle as clean as possible, swabbed it with a 10 per cent solution of phenol, which he stated did not injure the vessels or ureter and was strong enough to destroy nerve fibrils missed by the dissection. Phenol also reveals any nerve fibrils that may have been overlooked, and they can then be severed if it is so desired.

Secretion of Urine.—Snapper[27] stated that urine is formed only by the combined action of different physiologic processes in the kidney in which the functions of the glomeruli and tubules are separated completely. It has been proved beyond doubt that in the glomeruli an ultrafiltrate of the blood plasma is formed. The glomerular filtrate contains all crystalloid substances of the blood plasma in the same concentration in which they are present in the blood, but the colloids, especially the proteins, do not pass through the glomerular membrane. In the tubules a reabsorption of water and different substances takes place. During passage through the tubules the original glomerular filtrate is changed into definite urine. The study of the rate of excretion and concentration of certain substances, which pass into the glomerular filtrate, are not reabsorbed in the tubules and are not excreted in the tubules, has shown that an astounding quantity of glomerular filtrate is filtered off per minute. This quantity varies between 110 and 170 cc. per minute. From 97 to 99 per cent of the water of this glomerular filtrate must be reabsorbed in the tubules. Neither this rate of filtration in the glomeruli nor this excessive reabsorption in the tubules is impossible, as different experiments and calculations have demonstrated. The creatinine and inulin methods by which these data have been obtained have withstood criticism successfully. As a physical ultrafiltration of the blood plasma takes place in the glomeruli, blood pressure must be important for the function of the glomeruli.

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[27] Snapper, I.: The Pathological Physiology of the Secretion of the Urine, Kong. d. internat. Gesellsch. f. Urol. **6**:575-627 (Sept.) 1936.

The permeability of the glomerular membrane is to be compared with that of a collodion membrane. Substances with a high molecular weight are retained; substances with a low molecular weight pass. As a rule it may be stated that substances with a molecular weight of less than 40,000 appear in the glomerular filtrate, whereas colloids with a molecular weight of more than 60,000 are retained in the blood.

In case of renal insufficiency the composition of the urine and blood may be fundamentally changed. For a normal functioning of the kidneys, a normal composition of the blood plasma is necessary. Changes in the composition of the blood may be followed by serious disturbances of the function of the kidneys, so-called extrarenal uremia. A decrease of the protein content of the blood plasma and of the sodium and chloride content of the blood plasma may both have an adverse influence on renal function. The innervation of the kidney is of great importance in renal function. Reflex anuria may be explained in this way. It is still doubtful whether operations on the nerve supply of the kidneys improve the functions of the diseased kidney.

Urine is a supersaturated solution of many substances. Different substances, practically insoluble, are present in solution of the urine in large quantities. This problem is of great importance in the prevention of the formation of stones. The hydrotropic action of different organic constituents of the urine is considered. Urea and hippuric, salicylic and phenylglycolic (mandelic) acid, and other substances often present in the urine increase the solubility of calcium salts, especially of calcium oxalate. Besides this direct hydrotropic action, the stabilizing influence of these substances on the colloids of the urine is of importance in the prevention of the formation of stones.

URETER

Anomaly.—Malgras[28] said that the extravesical opening of a ureter in the female ordinarily produces a picture of incontinence that is so characteristic that it will immediately suggest the correct diagnosis. It is a permanent incontinence, existing from birth, although micturition is normal. In cases in which the orifice of the ectopic ureter is discovered, retrograde pyelography will make it possible to determine to which kidney it belongs and also will reveal whether there is a double kidney, as is usually the case. Inability to discover such an orifice, however, should not be sufficient grounds for discarding the diagnosis of extravesical ureter if the clinical syndrome is clear. In that case an attempt should be made to demonstrate the abnormal kidney corresponding to this ureter. At present urography seems to be the most precise method for bringing out this evidence, provided more is not demanded of it than it can give. It makes it possible to affirm the existence of a supernumerary pelvis when such an organ is made visible by some opaque medium, but it does not justify the denial of such a pelvis when this is not revealed in the film.

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[28] Malgras, P.: Abouchements extravésicaux de l'uretère chez la femme, J. d'urol. **42**:269-301 (Sept.) 1936.

If a double kidney is demonstrated, heminephrectomy is the operation of choice, provided the arrangement of the vascular system permits it. If retrograde pyelography does not determine beyond a doubt to which kidney the ectopic ureter belongs, operative measures will reveal whether, in accordance with Weigert's law, the ureter opening lower down corresponds to the upper pelvis. To obtain this proof, the ureter under suspicion is incised longitudinally, and a catheter is passed from above downward; the point at which the catheter appears at the perineum will then give the site of the ectopic orifice.

Ectopic ureters are particularly prone to be the seat of acute infections which simulate pelvic suppuration of genital origin. Mistaken diagnoses due to this similarity of symptoms have been responsible for many useless laparotomies performed by general surgeons, who have not taken into account the significance of this particular type of incontinence.

Derbes and Dial[29] reported 2 cases of postcaval ureter in man, bringing the total number of cases in the literature to 14. Postcaval ureter in man was first described in 1893. Since then 11 cases have been reported.

These authors observed postcaval ureters in 2 adult cadavers. In each case the lower portion of the right renal pelvis and upper portion of the ureter were dilated and thin walled. The ureter passed behind the inferior vena cava at the level of the third lumbar intervertebral disk, at which point it was definitely constricted. It then passed forward between the aorta and the vena cava and thence downward, forward and laterally across the anterior aspect of the latter vessel. From that point, its course and entrance into the bladder were normal.

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[29] Derbes, V. J., and Dial, W. A.: Postcaval Ureter: Two Cases, J. Urol. **36**:226-233 (Sept.) 1936.

In the 14 reported cases, the condition was found in an acardiac fetus, in 2 infants and in 11 adults. Hydronephrosis was present only in the adults, but it was found in all these except 1. In that instance the ureter was encircled by a venous ring at the pelvic brim. It is to be inferred, therefore, that duration is an important factor in the production of hydronephrosis when associated with this anomaly. The hydronephrosis is produced by kinking and stricture attributable to the anomalous course of the ureter, by pressure of the vena cava or by any or all of these factors.

In only 1 of the reported cases was diagnosis of the anomaly made before death, that being made at operation for stone and relief of hydronephrosis. Derbes and Dial stated that they are aware of no way by which a positive preoperative diagnosis can be made, though postcaval ureter should be kept in mind in all cases of hydronephrosis in which the etiology is obscure, as symptoms and sequelae would be similar to those of ureteral obstruction from other causes.

The type of anomaly itself immediately suggests that ureteral dilation or nephropexy will not relieve the hydronephrosis produced by it. If operation becomes necessary and a postcaval ureter is found, a plausible treatment might be transposition of the ureter from its position posterior to the vena cava to an anterior position with ureteropelvic anastomosis.

Calculi.—Grant[30] reviewed 100 cases of ureteral stone and arrived at the following conclusions: A large percentage of stones, probably more than 40 per cent, will pass without any treatment except relaxation of the ureter by medicinal means. Another 45 per cent will pass following ureteral manipulation. Ureteral manipulation, even with catheters, is not without danger. Frequently they cause swelling, which may only increase the obstruction, and perhaps, even more often than is suspected, the ureter may be perforated. Perforation below the stone may not cause any grave disturbances. In the case of infected kidneys, when it is possible to introduce a catheter beyond the stone, indwelling catheter and lavage prior to operation are a decided advantage. Likewise, they enable the surgeon to study the function of the kidney and to determine the choice of operative procedure.

Injury.—Wildbolz[31] proved by an experimental study that if the ends of a ureter which has been cut transversely are properly sutured together so that stricture does not occur, the ureter resumes its functions and that the kidney above the anastomosis functions normally. Considerable experimental work has been done on this subject, all of which suggests that hydronephrosis develops above the line of suture. Most of the experimental animals have been killed several days or weeks after operation in order to examine the kidneys, and most of the various investigators have concluded that hydronephrosis was developing because of dilatation of the ureter and pelvis above the line of suture. In most of these experiments the ability of the ureter to hypertrophy had been overlooked.

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[30] Grant, Owsley: Cautions in the Treatment of Ureteral Calculi, Ann. Surg. **103**:935-940 (June) 1936.

[31] Wildbolz, Egon: Die quere Ureternaht und ihre Folgen. Experimentelle Studie, Ztschr. f. urol. Chir. u. Gynäk. **42**:56-79, 1936.

Wildbolz in his experiments exposed the ureter through a transperitoneal incision, cut it through just below the renal pelvis, resutured the ends together with a circular suture and closed the wound without drainage. This procedure was carried out on 11 dogs. One died the day after operation and 1 a month later. In neither was there infection of the field of operation. A pyelogram was made every six months on the remaining dogs, which were in excellent physical condition. The dogs were killed at the end of two years. In 4 a stricture of the ureter was found at the point of suture, and above that marked hydronephrosis had developed. This hydronephrosis could also be seen in the pyelograms. In 5 dogs good results were obtained. The kidney above the suture was normal, and there was no atrophy of the parenchyma on microscopic examination. The ureter above the suture was dilated, as was also the pelvis in some of the dogs. The wall of the ureter and pelvis was always thickened and the muscularis hypertrophic.

In conclusion, Wildbolz stated that suturing of the transversely cut ureter when properly done does not always cause hydronephrosis. This procedure could readily be used in surgical work in cases in which it is necessary to cut the ureter or it is cut accidentally.

Transplantation.—Hinman and his associates,[32] from a study of uretero-intestinal implantation, stated that peritonitis rarely occurs as a result of contamination by the contents of the bowel or by urine at the time of operation when obvious precautions are followed. Leakage from the bowel or the ureters after operation is the common cause of peritonitis. Leakage occurs when the anastomosis is faulty and the ureter has not been sutured securely into the opening of the intestine, when anchoring sutures tear or slough out, when a suture punctures the bowel (fecal fistula) or the ureter (urinary fistula) and on necrosis of a portion of the intestine or of the transmural portion of the ureter.

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[32] Hinman, Frank; Murphy, W. K.; Wyman, Brent; McCorkle, H. J., and Benteen, F. H.: An Experimental Study of Uretero-Intestinal Implantation, Surg., Gynec. & Obst. **62**:909-917 (June) 1936.

The blood supply of the bowel or ureter must not be tied off by sutures or impaired by too great constriction, which may occur when suturing is done in layers.

Infection of the abdominal wound from contamination at the time of operation is more likely to result than peritonitis. Abscesses in the abdominal wall may rupture to the inside and produce peritonitis.

Implantation by any method which requires that the bowel be opened at the time carries considerable risk of localized inflammation of both the bowel and the ureter. Localized peritonitis may clear up or become general. An abscess may be absorbed, or it may rupture into the cavity and then produce peritonitis. Periureteritis may produce urinary obstruction, or the infection may ascend to the kidney. Localized inflammation may lead to anemic necrosis of the bowel or ureter, leakage and, ultimately, peritonitis. Inflammation at the site of implantation may result from temporary leakage after operation, and this probably is the most frequent cause.

Counseller[33] has found that the satisfactory results that have been obtained after transplantation of both ureters to the pelvic portion of the colon for exstrophy of the bladder have formed a stimulus for similar surgical treatment of women when the urinary bladder has been rendered useless by traumatism or disease. Counseller in his article refers particularly to huge vesicovaginal fistulas, chronic interstitial cystitis with secondary contraction of the bladder and certain carcinomas of the bladder.

The surgical technic employed follows the principles of C. H. Mayo and Coffey. The right ureter is transplanted first, and the left ureter, not earlier than two weeks later. Thirteen illustrative cases are reviewed briefly. There were three deaths. As the urinary bladder is obviously the best receptacle for urine, bilateral uretero-enterostomy should not be undertaken without serious consideration of all circumstances in each case. Surgical risk is minimized by giving attention to the general condition of the patient; the status of the upper part of the urinary tract, with regard to the presence of obstruction, infection or reduced function of the kidneys; the presence or absence of pelvic cellulitis which involves the lower ends of the ureters; previous surgical procedures on the pelvis, which may have resulted in fixation of the important structures, and the preoperative preparation of the patient. The risk of operation is definitely increased if one attempts to transplant grossly abnormal ureters to the bowel. At times preliminary nephrostomy may be utilized as a procedure to reduce infection and relieve obstruction to the kidneys prior to ureteral transplantation. Occasionally such a procedure is necessary after treatment of carcinoma of the uterine cervix with radium. Intravenous urography is definitely helpful in determining the status of the kidneys prior to operation.

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[33] Counseller, V. S.: Bilateral Transplantation of the Ureters of the Female, Proc. Staff Meet., Mayo Clin. **11**:699-701 (Oct. 28) 1936.

PROSTATE GLAND

Prostatectomy.—Schanz[34] reported 323 new cases in which operation has been performed by Kirschner since 1931. In the total group of 745 cases, there were 574 of adenomatous hypertrophy of the prostate gland. Most of the patients were in poor general health when first seen.

Radical operation was performed on all the patients who were strong enough. Kirschner preferred the perineal route and gave the following reasons for this: When prostatectomy is performed by the suprapubic route, the bladder must be opened twice, and also the prostate gland is situated much deeper than when the perineal approach is employed. The perineal method avoids opening the abdomen and thus diminishes the incidence of pulmonary complications. Bleeding can be controlled easier, and there is no need for a packing. The secretions from the incision drain more readily from the perineal wound than from the suprapubic, and the sphincter muscles can be preserved more readily. In 292 (51 per cent) of Kirschner's cases the perineal route was employed. The mortality was 4.2 per cent, and the results at the time of the patient's dismissal and on reexamination from one to four years later were the best of all methods of treatment. Contraindications to the radical operation are serious disturbances of the circulation or renal function, cachexia, diabetes and perivesical infection.

For the patients who were comparatively well but who could not stand radical operation, suprapubic drainage was instituted. This was the treatment until 1932 and was employed in 94 cases (7 per cent). Since then the patients who could not stand radical operation had been treated by transurethral electroresection; this was used in 42 cases (7 per cent). The great disadvantage of transurethral methods is the risk of leaving a malignant prostate gland without realizing it. Schanz estimated this risk at about 15 per cent. That is the principal reason why Kirschner preferred radical operation. There were 4 deaths (12 per cent) after transurethral electroresection. The results were not as good as those of perineal prostatectomy. The high mortality is due to the fact that all the patients in good general condition underwent prostatectomy.

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[34] Schanz, F. E.: Ueber Behandlung und Behandlungserfolge des Prostataadenoms, Ztschr. f. urol. Chir. u. Gynäk. **42**:169-198, 1936.

One hundred and forty-six patients (26 per cent) were too ill to undergo any operative intervention. For the permanent treatment of inoperable conditions, the indwelling catheter in the urethra is superior to suprapubic drainage. The catheter that is put in after ligation of the vas deferens to prevent epididymitis can be worn for years if properly cared for. Most of the patients on whom suprapubic drainage was instituted were uncomfortable and dissatisfied.

Haim[35] stressed the superiority of perineal prostatectomy over all other procedures. He stated that there are only two reasons why it is not used as widely as it deserves: The technic is more difficult, and surgeons who employ the suprapubic method, which is easier to do, are diffident. The advantages of the perineal method are that less shock and fewer cardiac and pulmonary complications result and that there is a reduction in the number of cases of thrombosis and embolism.

To increase the use of perineal prostatectomy, Haim recommended standardizing and simplifying the procedure in order to rule out the possibility of postoperative incontinence and fistulas. These complications occur rarely in the hands of a surgeon skilled in perineal prostatectomy, and when they do occur it is usually in cases of carcinoma. He recommended going in between the anal sphincter and the rectal wall, so that the rectum may be seen during the operation, and the injection of some fluid into the prostate gland between the adenoma and the capsule to make enucleation easier.

Lumb[36] reported a technic for suprapubic prostatectomy, its main advantages being the facility with which the floor of the bladder can be reformed and the definite approximation of trigonal tissue to the divided posterior urethra. After an extended trial, this operation has fulfilled its purpose, and its value is enhanced by its simplicity, since complicated instruments and illuminated retractors are not needed for its performance.

Several advantages have resulted from this method: The trigonal flap is stretched evenly over as large a portion of the posterior aspect of the prostatic cavity as it can be made to cover. There is maximal approximation of the trigon to the posterior urethra, intimate contact between the whole of the trigonal flap and the underlying wall of the prostatic cavity and reduction of hemorrhage. The floor of the bladder, when reformed, closely approximates normal.

A gum elastic coude catheter having two eyes is threaded with two moderately stout silk threads about 18 inches (46 cm.) long, so arranged that about 3 inches (7.6 cm.) of each projects from each eye. The catheter is passed into the bladder, and the distending fluid is injected. A wooden spigot closes the catheter, and a sterile towel is arranged on which the outer ends of the silk threads rest beside the catheter. A pair of small artery forceps is attached to one thread and a pair of large forceps to the other, so that the threads may be distinguished subsequently, or silk threads of different color may be used.

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[35] Haim, Emil: Gedanken zur Behandlung der Prostatahypertrophie, Wien. med. Wchnschr. 86:1004-1007 (Sept. 5) 1936.

[36] Lumb, Norman: Trigonal Loop-Traction in Suprapubic Prostatectomy, Brit. J. Urol. 8:257-265 (Sept.) 1936.

A midline incision is preferred, though a transverse one may be adopted equally well; the peritoneum is displaced gently upward, exposing the bladder, which is opened at its highest point. The wall of the bladder is punctured, and a suction tube is used to evacuate the contents. Great care is taken to avoid opening the cellular tissue in front of the bladder.

The ends of the two silk threads which are in the bladder are unthreaded from the eye of the catheter; a small forceps is placed on one and a large forceps on the other, and the catheter is withdrawn. Two separate silk threads thus traverse the urethra from the meatus to the bladder. The prostate is enucleated as expeditiously as possible. Dry gauze from a 3 inch roll is lightly packed into the cavity to check hemorrhage. A self-retaining retractor is inserted, and the gauze is withdrawn.

A fine silk suture, 18 inches long, is made through the trigon in the middle line, about ½ inch (1.3 cm.) behind the raw edge, thus securing a firm hold on it. The ends of the suture material are tied to the bladder end of one of the silk threads previously mentioned and drawn through the urethra to the external meatus. When the threads are pulled tight a triangular flap of trigon is drawn down, largely obliterating the posterior portion of the prostatic cavity and diminishing the bleeding. The weight of the forceps attached to the silk thread will be found sufficient to keep the flap in position at this stage, and the indwelling catheter is inserted next. A flute-ended india rubber catheter, size 22, with two lateral openings, is used for this purpose. After lubrication it is readily drawn into the bladder by the second silk thread, which is secured to its tip. The silk thread is removed, and a stout silkworm gut stitch is attached instead to the tip of the catheter, the ends being held in a forceps. This is used later for suspending the catheter in its final position within the bladder.

At this stage bleeding is considerably diminished, and the remainder of the plastic portion of the operation consists in inserting the anterior obliterating stitches. These may be made more effective by using the infolding method to be described, as they then tend to diminish pocketing in the anterior part of the cavity during healing. A wide hold is taken with the boomerang needle, and the catgut stitch is drawn through. The two free ends of catgut are made to cross to opposite sides of the prostatic cavity, where each is threaded on a needle, a portion of the rim is picked up and the ends emerge once more into the bladder. On tying the ends, infolding takes place and the edges are well inverted.

The catheter is carefully adjusted so that its lower lateral eye lies just at the entrance to the torn posterior urethra, thus draining the prostatic cavity completely, and a small drainage tube is placed in the bladder. Closure of the wound in the bladder is carried out in the usual way, with an inverting stitch, followed by a second layer of fine catgut. The drainage tube should lie at the upper end of the incision into the bladder and be firmly gripped; the loop of silkworm gut suspending the catheter emerges immediately below it. The catheter is left in place for from ten to twelve days and then removed, together with the traction stitch from the trigon.

Resection.—Thompson and Buchtel[37] reported a series of 200 consecutive cases of prostatic hypertrophy in which treatment involved transurethral resection of 25 Gm. or more of prostatic tissue; 140 patients, or 70 per cent, had suffered from complete urinary retention. Eighty-eight patients, or 44 per cent, were aged 70 years or more.

Thorough removal of all adenomatous tissue which encroaches on the neck of the bladder, particularly in the anterior half, so that all inverted V deformity is eliminated, and careful hemostasis during the progress of the operation are important points in technic. An operation must not be prolonged or shock may result; in Thompson and Buchtel's experience, patients withstand a two stage or three stage procedure, each of short duration, much better than a single operation which lasts more than one hour. The bladder must not be allowed to become overdistended at any time during operation or during the postoperative course or fever may ensue. If the functional result is not good immediately after drainage by inlying catheter has been discontinued, judicious intermittent catheterization or early reoperation is essential to an uncomplicated convalescence.

Replies to letters of inquiry indicate a high degree of satisfaction among the patients. Sixteen patients (15 with benign lesions and 1 with a malignant lesion) have returned to the clinic for reoperation six months or more after their dismissal. One of these patients was subjected to perineal prostatectomy, while the others preferred to undergo further transurethral resection. The mortality in the series was 1.5 per cent.

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[37] Thompson, G. J., and Buchtel, Henry: Transurethral Resection of the Large Prostate: Review of Two Hundred Cases in Which Twenty-Five Grams or More of Tissue Was Removed, J. Urol. **36**:43-56 (July) 1936.

It occurred to Emmett[38] that because of the hemostatic quality of posterior pituitary it might be of value in the reduction of hemorrhage in transurethral resection of the prostate gland. Resection at the Mayo Clinic is performed by means of the direct vision, cold-cutting resectoscope, in which an electric current is employed only to fulgurate individual bleeding points after tissue has been removed by the tubular knife. Because of the fact that a lens system is not employed, bleeding causes little difficulty with vision. However, it is important that as little blood as possible be lost during and after the operation; hence, any method that might aid in conservation of blood is worthy of investigation.

A rigid needle has been constructed, with a shaft long enough to project through the full length of a Braasch direct vision cystoscope. The needle proper is of 21 gage and is ⅞ inch (2 cm.) in length; it has a small, circular hilt where it joins the shaft to prevent it from being inserted any farther than its length into the prostatic tissue. At operation an injection is made into each of the three prostatic lobes. To make the injection, the heel of the cystoscope is placed against the portion of the lobe into which the solution of posterior pituitary is to be injected, and the cystoscope is maneuvered so that it forms, as nearly as possible, a right angle with the surface of the lobe. This is done in order to assure the injection of material well into the tissue rather than just having the needle slide under the mucosa. This is the most difficult part of the technic of the injection. The needle is then introduced blindly, as one implants radon seeds, and is inserted into prostatic tissue to the hilt. A third of the total dose of posterior pituitary is injected into each lobe. A total injection of from 1 to 3 cc. of solution of posterior pituitary of double U. S. P. strength has been used, but 2 cc. seems to be about the proper amount. In 2 cases a mixture of 1 cc. of solution of posterior pituitary and 1 cc. of ergotamine tartrate was used.

In 31 consecutive cases in which resection of the prostate gland was performed, the foregoing method of injection was employed. Spinal anesthesia was used in all the cases. In 29 cases injections of solution of posterior pituitary alone were given, the total dose varying from 1 to 3 cc., whereas in 2, injection of a combination of 1 cc. of solution of posterior pituitary and 1 cc. of ergotamine tartrate was employed.

Results of injection are interesting. In 25 cases results were satisfactory; in 7 of these no bleeding was encountered at the operation, which was terminated within thirty or thirty-five minutes. In the remaining 18 cases the wash water was colorless for periods varying from twenty-two to forty-seven minutes. The average length of time for the water to remain clear was about twenty-seven minutes. In these cases, after this period vessels began to bleed in varying degrees from slight to rather sharp bleeding. All bleeding was easily controlled with the usual fulguration. In the remaining 6 cases, experience in which was not classed as satisfactory, the results were as follows: In 2 they were fair; that is, at no period was the wash water absolutely colorless, but instead it was only a light pink for about twenty to twenty-five minutes, after which the usual bleeding occurred; in 1 of the remaining 4 the wash water was colorless for ten minutes, and then moderate bleeding occurred, while in the other 3 it was difficult to say whether the posterior pituitary had any effect.

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[38] Emmett, J. L.: Preoperative Intraprostatic Injection of Pituitrin in Transurethral Resection: Preliminary Report, Proc. Staff Meet., Mayo Clin. **11:** 619-622 (Sept. 23) 1936.

Kretschmer[39] stated that his position in the discussion of transurethral resection can best be summarized by saying that during the past fifty-one months he performed prostatectomy only once and that during the same time he refused resection to only 1 patient.

The period of hospitalization is much shorter with resection than it is with surgical prostatectomy, and while this fact may not be of much importance to a small percentage of patients, all things being equal, it is an economic factor of enough importance to demand attention.

The number of cases in which preliminary suprapubic cystostomy is employed has become fewer and fewer. During the past three months preliminary cystostomy has been done only once. On the other hand, Kretschmer expressed the belief that cystostomy is indicated when drainage by catheter fails because of chills, fever, pain or bleeding, or when small stones with severe infection or large stones are present.

The number of patients with cardiac conditions seeking relief has increased definitely. Whereas, in the days of surgical prostatectomy about 35.8 per cent of the patients suffered from cardiovascular lesions, a recent study of Kretschmer's cases in which resection was performed revealed cardiovascular lesions in 64.3 per cent, an increase of 28.5 per cent.

As Kretschmer's experience with resection widened, he performed operation in a certain group of cases without preliminary drainage by catheter. Heretofore all patients who had 4 ounces or more (120 cc.) of residual urine were given preliminary drainage. At present no preliminary drainage is employed in a case in which the residual urine does not exceed 6 ounces (180 cc.), provided the urine is clear, the renal function normal and the heart and lungs in good condition. Preliminary cystoscopy is no longer carried out as a routine; once the diagnosis of prostatic obstruction has been made, the type of enlargement is determined when resection is performed. The exceptions to this rule are: in case the history is not typical for prostatic obstruction, if there is a history of one or more attacks of hematuria and if the cystogram reveals a filling defect.

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[39] Kretschmer, H. L.: Transurethral Resection, Ann. Surg. **104**:917-933 (Nov.) 1936.

In Kretschmer's series of cases in which resection was done, a second resection was performed in 10.6 per cent and a third one in 3.7 per cent.

Before the technic of resection was completely mastered, hemorrhage at operation was at times a serious problem, but with experience this untoward occurrence has become less of a problem, although occasionally a serious hemorrhage occurs no matter how careful one is. Careful search for the bleeding point should be made and its immediate control effected. Secondary bleeding, which was never severe, occurred in 19 cases on the tenth to the fourteenth day. Clots, when present, were evacuated with the Bigelow pump, and the bladder was washed out with a warm solution of silver nitrate. In most of the cases this controlled the bleeding, but when this procedure failed the resectoscope was introduced, and the bleeding point was fulgurated or excised. Late hemorrhage occurred in 14 cases at periods varying from three months to two years after resection. In the patients who were reexamined, enlarged vessels were found around the orifice of the bladder and in the prostatic urethra. These were destroyed by fulguration. An interesting fact is that these late hemorrhages occurred in patients with large prostate glands.

The incidence of epididymitis has diminished as experience with resection has grown. In 15 per cent of the first 117 cases this complication occurred, and vasectomy was done as a routine, an operation no longer employed, as this complication is very rare.

There has been no instance of complete incontinence in Kretschmer's series of 804 cases in which resection was performed. Shortly after leaving the hospital a small number of patients have had difficulty in holding urine. This was due not to incontinence but to urgency and imperative urination. Continence of urine was eventually recovered. In a few instances the patients would lose a few drops, but this was temporary, and as the infection cleared up the condition rapidly disappeared. In 2 instances the loss of a few drops of urine was due not to incontinence but to stricture of the urethra.

The mortality has fluctuated from time to time, depending in part on the type of cases and whether or not one wishes to refuse resection to many of the patients who are considered bad risks, which Kretschmer has not done. His records show that he has performed 184 resections with but 1 death—a mortality of 0.54 per cent. The 804 patients who were operated on included a large number who were classed as bad risks, and the mortality for the entire series was 3.9 per cent.

Beer[40] stated that these new methods of transurethral resection are of use in the following conditions:

1. Contractures of the neck of the bladder, which in years past were excised by a wedge-shaped excision from above through the bladder. These can be cut with a point or loop electrode, an ordinary operating cystoscope or a resectoscope being used. Complete relief from symptoms results. This is a great improvement over the cold punch operation or the suprapubic excision. The latter procedure or approach, however, may be useful when the exact physical status of the neck of the bladder is not accurately visualized.

2. Obstruction caused by carcinoma of the prostate gland. This condition also lends itself satisfactorily to transurethral resection, which may be repeated as a new obstruction develops. The tissue removed during such an operation is often helpful in establishing the correct diagnosis.

3. The ordinary and usual type of prostatic hypertrophy or adenoma. When it comes to these conditions the field of transurethral resection has no limitations for some enthusiasts and definite limitations for others. Included here as a subgroup is moderate prostatic enlargement associated with mild symptoms of frequency and questionable obstruction and a small amount of residual urine. No experienced surgeon would feel justified in performing prostatectomy on a patient with a condition of this type. Such patients present a definite potential field for transurethral resection and may represent a large proportion of the total in most published series of resections. The frequency, and perhaps the infection, do not always disappear but may be made worse after excision of some prostatic tissue, despite a reduction of the residual urine. In these cases the lesion is definitely a beginning prostatic adenoma and is not to be considered with those cases in which prophylactic resection has been performed before any definite complaint has developed. It is doubtful whether resection affords the patient the expected relief with any regularity. If the subjective complaints are well developed, one is justified in attempting to give relief by resection, even though it may be only temporary and incomplete. Correct diagnosis here, as always, is essential.

In addition to those patients with mild symptoms referable to the prostate gland who frequently are worse off after resection, there are two other groups of patients who have definite prostatic adenoma that must be discussed: those with moderately large, bilobed, trilobed or single lobed prostate, and those with large, more or less trilobed or bilobed hypertrophy. In localities in which no pressure is brought to bear on the surgeon by competitors, the patient or his friends, the opinion is gradually developing that the last-mentioned group, with large, succulent adenomas, should be treated radically and definitively by prostatectomy or enucleation of the adenoma, either by the suprapubic or by the perineal approach. This attitude seems to be based on a great many factors, without denying that if the "resectionist" is patient he can whittle away a fair amount of the largest prostate in one or more sessions.

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[40] Beer, Edwin, in discussion on Kretschmer,[39] pp. 928-931.

The two stage suprapubic prostatectomy has gradually assumed the status of an almost minor procedure, with a low mortality, of 6 + per cent, which is usually incidental to cardiovascular disturbances, and with complete cure without chance of recurrence, if properly performed. On the other hand, the transurethral approach for the large adenoma frequently is followed by a whole group of complications, such as primary or secondary hemorrhage into the bladder, which necessitates repeated evacuation of clots, infection of the bladder and more or less complete resection of the base of the prostate gland which frequently, much more frequently than is reported, may turn the scales against the patient, not to mention the various instrumental damages and perforations that are reported by competent instrumentalists. Because of the prolongation of the necessary instrumental work and the various complications, the mortality is likely to be definitely higher than with the transurethral approach with a two stage suprapubic enucleation. This is Beer's experience. He stated that if the statistics on prostatic adenoma alone were considered, the data of other clinics would probably bear him out. The trouble with most statistical studies along these lines is that they include the results of operation for simple contracture, small, almost symptomless hypertrophy and moderate-sized but definite adenoma of the prostate gland as well as extensive hypertrophy and of prophylactic excisions, done perhaps because of incorrect interpretation cystoscopically.

In the moderately enlarged prostates, as opposed to the very large adenomas, which weigh an ounce (28 Gm.) or more and are as large as one to three or more lemons, there is a definite field of usefulness for transurethral resection, even though repeated sessions may be required before the patient can void and be comfortable and even though, as time goes on, one may see more and more of these partially removed adenomas redevelop and produce recurring symptoms, which is a rare sequela to a properly executed complete enucleation. There is no doubt that in this group of moderately enlarged prostates one is justified in using transurethral resection, if the patient requests it and especially if he is a poor surgical risk because of poor renal function, coronary disease, diabetes, etc.

According to Beer, a careful follow-up of the cases in which resection was done leaves much to be desired.

Beer stated that he was impressed by the reports of large numbers of cases in which resection has been performed and yet continued treatment, soundings, irrigations of the bladder, etc., are necessary; these are practically never required when a proper prostatectomy has been performed. There is no doubt that most patients void more readily after resection and have much less residual urine than before the operation, but a large number of patients are not absolutely and definitely cured, as they are after a complete enucleation of the adenoma. Pyuria, frequency and dysuria often persist for months or permanently in every series of cases in which a really careful check is maintained.

That transurethral resection of the prostate gland has become an unusually popular procedure, without due selection of cases, cannot be denied.

Lower[41] stated that transurethral resection of the neck of the bladder for obstruction has been revived in the last few years, probably because of improvements in instruments and electrical apparatus. Not only are the median bars and the sclerotic obstructions resected now, but the use of transurethral resection is being extended to include a much wider field, especially in the treatment of prostatic hypertrophy.

In what cases should this procedure be used? Experience has taught that its scope of usefulness is much wider than was formerly thought, but again the danger of broadcasting the simplicity of the operation should be emphasized. However, it is true that it carries with it a low mortality, and so far the postoperative results in most cases have been good. Among approximately 500 resections which have been performed at Lower's Clinic, the mortality has been 1.8 per cent, including a series of 225 cases in which no deaths occurred. These were not selected cases, but included all types. Among the patients were many feeble and elderly persons.

As wider experience has been gained, larger and larger amounts of tissue have been removed. Another advantage of this operation is that a second or even a third operation may be performed if necessary without any special risk.

Bleeding is becoming inconsequential. When the procedure was first used, bleeding occurred frequently, but Lower has found it necessary to open the bladder in only 1 case.

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[41] Lower, W. E., in discussion on Kretschmer,[39] pp. 931-932.

The incidence of epididymitis in the entire series was 6.8 per cent, and the average stay in the hospital was less than seven days; this economic factor is of considerable importance, especially in these times.

Cabot[42] stated that in the first place there are various methods of whittling out the prostate through the urethra. His notion is that the instruments will probably be greatly modified. The problem should be discussed without prejudice. Beer has perhaps a case to prove; he performs chiefly prostatectomy. Kretschmer has a case to prove; he does chiefly resection. Cabot stated that he has no case to prove.

In reference to Beer's remarks on the unfortunate results of resection, Cabot stated that if the truth were told, the statistics would be loaded handsomely with the unfortunate results of prostatectomy. The mortality of prostatectomy, which up to the last few years was over 50 per cent in the hands of the occasional surgeon, has never been less than 20 per cent the country over, and is not now. Prostatectomy is an operation for experts, whether the suprapubic, the transurethral or the perineal method is used. The discussions should be confined to the results obtained by experts, not to the results obtained by surgeons who operate on the patient not for prostatic obstruction but for a hundred dollars. That will cause damage, and does, in every field of surgery. It is not fair to the operation.

Six years ago, more than half the patients on Cabot's surgical list were to have prostatectomies, but he has not done a prostatectomy in three years. There have been only 3 or 4 done in the last two years at the Mayo Clinic.

The age group is interesting. Of 1,922 consecutive prostatectomies done between 1924 and 1932, 5.6 per cent were performed on patients more than 75 years of age. Of the last 700 transurethral resections done up to Jan. 1, 1936, 15.7 per cent were performed on patients over 75.

It is frequently suggested that this operation is being performed chiefly for patients who do not need it, which is not entirely true. Patients who are more gravely ill are being operated on with better results.

It has been the habit at the Mayo Clinic, and it is not a bad one, to keep all the tissue which the surgeon removes. About a year ago Cabot thought that it would be interesting in a series of 1,000 cases to take a fair average of the gross amount of prostatic tissue removed by suprapubic prostatectomy and to compare it with the gross amount removed by transurethral resection. The amounts removed by resection are approaching those removed by prostatectomy. The group of men at the Mayo Clinic who perform resections now take out almost as much tissue on the average as was taken out by prostatectomy five years ago. It thus appears that the transurethral route is becoming the method of prostatectomy. If the same amount of skill for this method is insisted on as is shown by the experts using the suprapubic or the perineal route, resection has much to offer and will cover a large portion of the field.

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[42] Cabot, Hugh, in discussion on Kretschmer,[39] p. 932.

Carcinoma.—Chauvin and Mosinger[43] asserted that the histogenesis of malpighian tumors of the prostate and other viscera which, like the prostate, possess no paramalpighian structure, is a subject of the greatest interest and that three hypotheses have been suggested to account for it. 1. The tumor develops on an island of malpighian metaplasia, such as can be observed in the biliary and respiratory tracts and in the body of the uterus after a chronic inflammatory process. 2. The tumor develops on a dysembryoplastic soil. 3. It is the result of the direct transformation of normal epithelium into a cancerous tissue of malpighian structure.

In order to choose among these hypotheses, the authors undertook to discover the relative frequency of malpighian or paramalpighian islands in nontumorous prostates, in adenomas of the prostate and in epitheliomas in which glandular substance predominates. In a malpighian epithelioma of the prostate they found an adenomatous zone and an epitheliomatous zone, the latter in the center of the former. They were thus able to prove the coexistence of an adenomyoma of the prostate in which the hyperplastic process was doubled by the phenomenon of malpighian metaplasia and a malpighian epithelioma grafted on the adenomyoma.

It might have been thought, in view of the frequency of a malpighian metaplastic process in the purely adenomatous zone, that the epithelioma developed from a malpighian island. But a study of the epitheliomatous zone revealed conclusively that metaplastic malpighian trabeculae could arise directly from epithelial tubes that were themselves tumorous. Chauvin and Mosinger were able to demonstrate beyond a doubt the truth of the third hypothesis, that of immediate tumor metaplasia; but that this process occurs in a predisposed territory was shown by the frequency of metaplastic islands disseminated in the adenomatous zone. In nontumorous prostates in which there was chronic prostatitis, they found islands of malpighian metaplasia developing often in contact with islands of inflammatory connective tissue. Of 6 prostatic epitheliomas of various structures, they observed malpighian islands lying in the midst of the tumor tissue in 3.

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[43] Chauvin, E., and Mosinger, M.: Sur les épithéliomas malpighiens de la prostate et leur histogénèse, J. d'urol. **41**:297-306 (April) 1936.

They concluded that malpighian metaplasia is observed in 32 per cent of cases of adenoma of the prostate and in an equal percentage of cases of prostatitis. The possibility of malpighian cancers developing secondarily from these islands must then be faced. However, the study of their own case of malpighian cancer and the frequency of malpighian islands in cancers of the prostate of different structure show that the malpighian aspect may appear even at the moment of canceration.

Uebelhör[44] stated that fairly uniform results are obtained in most clinics in the treatment of carcinoma of the prostate; namely, only a few lasting cures are obtained, but there is improvement in many cases.

The first question that Uebelhör discussed is: Why do so few surgeons use the perineal method, when Young and Wildbolz get such good results? The answer is easy; most surgeons use the suprapubic approach as a routine procedure, and when they perform perineal prostatectomy occasionally for carcinoma they have a great percentage of fistulas, incontinence and strictures, which discredits the method in their eyes. Uebelhör and the representatives of the Viennese school prefer the suprapubic route for prostatectomy, but Uebelhör expressed the belief that it would be wise to practice the perineal method also in order to be able to use it with success in suitable cases.

Radical operations have not found many followers. The shock to the patients is too great, and the chances of freedom from cancer are too unstable. Suprapubic drainage is not "the best of all methods" in these cases, as has often been quoted. Its use is justified only in cases of obstruction, in which it is competing successfully with transurethral resection. Uebelhör stated that roentgen therapy according to the Coutard technic or radium therapy in combination with surgical intervention is the most promising method. The remarkable variations in the course of the disease make estimation of the value of any new method of treatment difficult; for example, occasional patients survive more than four years after a definite diagnosis of carcinoma has been made, even in the absence of treatment.

Keyes and Ferguson[45] argued that the term "early" as applied to prostatic carcinoma covers that group of cases in which diagnosis cannot be made by rectal examination. The disease surely exists before it is palpable by rectum. There have been cures when the malignant growth was confined to a hypertrophied portion of the gland and the patient was fortunate enough to have undergone prostatectomy for the relief of the enlargement. The carcinoma, not having extended to the remainder of the gland, comes out with the adenoma, and its presence is unsuspected until shown on pathologic section.

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[44] Uebelhör, Richard: Bemerkungen zur Therapie des Prostatakarzinoms, Wien. med. Wchnschr. 86:1038-1044 (Sept. 5) 1936.

[45] Keyes, E. L., and Ferguson, R. S.: Early Diagnosis and Radical Treatment of Carcinoma of the Prostate, Brit. J. Urol. 8:346-352 (Dec.) 1936.

Because of the difficulties of recognition of this "early" prostatic carcinoma, Keyes and Ferguson removed material for biopsy by aspiration from all prostates in men aged more than 50 years whose glands were the least bit irregular. They reported on 2 series of cases in which biopsy specimens were secured in this manner. In the first series, consisting of 100 cases, biopsy was done by Ferguson at the Memorial Hospital. In 18 of the cases insufficient tissue was obtained to permit a diagnosis. In 59 of the others a diagnosis of carcinoma was made, and in 23 the tissue was found to be noncarcinomatous. Fifty-seven patients in whose prostates carcinoma was found have died of carcinoma. One of the survivors is living, but metastasis has occurred, and the other, who submitted to interstitial irradiation by the Ferguson technic, is alive and well. Those patients whose tissue was pronounced to be noncarcinomatous have remained free from the disease to date.

In a similar series of 33 cases in which tyros undertook to perform biopsy on specimens obtained by aspiration, no tissue or insufficient tissue was obtained in the first 14 cases, and the pathologist was not able to distinguish carcinoma until the twenty-fourth specimen. After that he found tumor cells in 10 cases in succession. As in the first series, in no case in which the specimen was reported as noncarcinomatous are symptoms of carcinoma of the prostate known to have developed.

The method employed by the authors for the radical treatment of carcinoma of the prostate is the implantation of gold radon seeds (each containing 2 millicuries of the radium emanation) into the tumor by means of an instrument devised by Ferguson. This permits the accurate placing of the seeds, the urethral and vesical mucosa and the normal tissues about the tumor being avoided.

Since first using this method in May 1931, Ferguson has studied 41 patients treated by his technic by himself and others. He groups them according to results as follows: "rectal touch doubtful, biopsy positive," 14 patients, 9 of whom are alive and well, 4 for more than three years; "touch and biopsy both positive," 27 patients, 4 of whom are alive and well from one to two years. The authors stated that this procedure, with its low mortality, promises to compare favorably with the total prostatectomy of Young.

Nitch[46] stated that conservative treatment of carcinoma of the prostate comprises radiotherapy, surgical procedures and surgical procedures combined with radiotherapy.

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[46] Nitch, C. A. R.: The Conservative Treatment of Carcinoma of the Prostate, Kong. d. internat. Gesellsch. f. Urol. 6:147-154 (Sept.) 1936.

The immediate results of roentgen treatment are often excellent, but the ultimate results are disappointing. In some cases the roentgen rays cause a rapid increase of the growth and dissemination. The best results are obtained by the five field maximal method of Holfelder-Reisner with a total depth dose of from 150 to 200 per cent on the prostate. The intensive split dose method of Levitt, now under trial, seems productive of better results. At present only 6 per cent of cures can be claimed for modern methods of roentgen therapy. The results of radium therapy are better, especially when applied in large doses to the rectal, vesical and urethral surfaces of the prostate. Before treatment is begun, a thorough clinical, biochemical and roentgenographic examination must be made, and a portion of the prostate should be removed by electroresection for microscopic examination. About 70 mg. of radium is used in the treatment as follows: Fourteen milligrams is applied to the posterolateral surfaces, 50 mg. to the vesical surface and 5 mg. to the urethral surface. Though only a few patients have been treated in this way, the percentage of cures has been 28 up to the present. The method is therefore worthy of an extended trial. When results of renal function tests are below normal, preliminary drainage of the bladder is necessary.

Conservative surgical treatment consists of suprapubic drainage, transplantation of the ureters and electroresection. Transplantation of the ureters into the large intestine is preferable to suprapubic drainage but can be performed only in carefully selected cases.

Electroresection is the best palliative measure for the relief of obstruction caused by growth at the neck of the bladder. It is of no value when the obstruction is due to invasion of the prostatic urethra. It is probable that in the future electroresection followed by some form of radiotherapy will be the method of choice in treatment of carcinoma of the prostate.

Schanz[47] recorded Kirschner's experience of nineteen years in the treatment of diseases of the prostate in surgical clinics of Königsberg, Tübingen and Heidelberg and reported the results of surgical treatment in 144 cases of prostatic carcinoma. He stated that the radical perineal operation is the ideal treatment for a prostatic malignant condition and is the only method that offers a possibility of permanent cure. Operation is performed only when the patient is in good general condition and when the growth has not extended beyond the prostatic capsule. Under these circumstances the difficulties of the operation are not too great, and there is hope of complete elimination of all the tumor tissue. In the early stage of the disease radical operation is superior to any type of treatment. Surgical removal of the gland is usually followed by roentgen therapy.

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[47] Schanz, F. E.: Prostatakrebs, Ztschr. f. urol. Chir. u. Gynäk. **42**:292-307, 1936.

Patients who do not present these ideal conditions for operation are usually treated by transurethral electroresection of sufficient extent to relieve urinary obstruction. The advantage of a free flow of urine is more important than the danger of a rapid increase in the growth of the prostate. Patients who are unable to undergo even prostatic resection are treated by an indwelling urethral catheter. Suprapubic drainage was instituted only in the cases in which none of these procedures were possible.

Leiomyoma.—Baretz [48] reported a case of leiomyoma of the prostate gland, making a total of 13 cases of this rare lesion reported in the literature. This type of neoplasm cannot be diagnosed clinically, but it should be borne in mind when a prostate gland, on palpation, is firm, elastic or somewhat unusual in consistence. The growth is benign, and it produces symptoms similar to those of benign hypertrophy of the prostate gland except for increased rectal symptoms. It can be distinguished from benign hyperplasia or sarcoma only by histologic study. It may involve only a small portion of the gland or may have entirely replaced it.

Cysts.—Emmett and Braasch [49] stated that the most common cyst of the prostate gland is the simple retention cyst. This type of cyst is probably produced by obstruction to drainage of the normal prostatic acini with subsequent dilatation or by the coalescing of smaller cysts by means of rupture of the wall of an adjacent cyst. Small symptomless prostatic cysts, which are 0.5 cm. in diameter or smaller, are rather common. Most prostatic cysts never produce symptoms. Emmett and Braasch collected all cases of prostatic cyst reported in the literature since 1925 and summarized them. A series of 14 cases is reported in which prostatic cysts 0.75 cm. in diameter or larger have been encountered.

Diverticulitis.—Heitz-Boyer,[50] on the basis of a complicated case, demonstrated the value of cystography and urethrography in the diagnosis and treatment of severe diverticulitis of the prostate gland.

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[48] Baretz, L. H.: Leiomyoma of the Prostate, J. Urol. **35**:664-667 (June) 1936.

[49] Emmett, J. L., and Braasch, W. F.: Cysts of the Prostate Gland, J. Urol. **36**:236-249 (Sept.) 1936.

[50] Heitz-Boyer, M.: Observation type d'un cas complexe de maladie diverticulaire, à forme de prostatite chronique hypertrophianta; avec opération et guérison des multiples accidents, J. d'urol. **41**:369-387 (April) 1936.

Intense chronic inflammation of the entire prostatic urethra was present, and manifestations of peridiverticulitis leading to chronic prostatitis had been superimposed. The prostatitis was of both the sclerotic and the hypertrophic type and caused the patient to drag out a miserable existence. Urethroscopy revealed the orifice of the diverticulum, rather high up and at the left of the verumontanum; from this opening fibrinous agglomerations, a sort of "diverticular expectoration," were expelled from time to time. Above the verumontanum there was a depression forming a kind of "grotto." Cystoscopy revealed stenosis of the neck of the bladder with a columnar effect, numerous depressions appearing between the columns, while the two urethral orifices were widely dilated. As a result of this complex pathologic condition, retention of urine had caused dilatation of the kidneys, the pelves of which were two or three times normal size, and colon bacilli were present.

Endo-urethral treatment was carried out, consisting first of the exenteration of the diverticulum and the establishment of a wide communication in the prostatic cavity, after which the neck of the bladder was resected. As a result of operation the patient now urinates normally, there is no residual urine and the exaggerated contractility of the muscle of the bladder and the stenosis of the neck of the bladder have disappeared. The vesicoprostatic junction has been reestablished in its proper funnel shape. The patient is cured functionally as well as anatomically. Heitz-Boyer felt that such a result is a clear demonstration of the value of modern urethroscopic and transurethral treatment.

Intraprostatic Injection.—O'Conor and Ladd[51] reviewed the literature dealing with the clinical procedure of direct injection of medicinal solutions into the prostate gland. All previous authors on this subject have inferred that the rationale of the procedure is based on the direct bactericidal effect of the injected solution for the organisms retained in the prostatic acini and ducts. Encouraging clinical reports on intraprostatic injection of solutions in cases of chronic prostatitis have recently extended and revived the interest in this subject. A careful survey of all these reports failed to reveal any published work in which data were given to show what tissue changes actually occur in animals when these solutions have been injected directly into the prostate gland. The experimental work presented by O'Conor and Ladd demonstrated the effects of simple needling of the dog's prostate gland, the changes after the injection of sterile physiologic solution of sodium chloride, distilled water and solutions of mercurochrome, silvol, metaphen, meroxyl, merthiolate and electrargol (a colloidal suspension of silver).

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[51] O'Conor, V. J., and Ladd, R. L.: Intraprostatic Injection: An Experimental Study, J. A. M. A. **107**:1185-1188 (Oct. 10) 1936.

The technic of injection was devised to avoid all trauma, and the glands were removed en masse after periods varying from two days to three months.

O'Conor and Ladd concluded that the trauma of simple needling of the normal dog's prostate gland is followed by an inflammatory reaction, with considerable subsequent fibrosis and glandular destruction. All the solutions injected into the prostate glands of a series of 31 dogs brought about relatively uniform changes. These changes varied only in severity and degree. It would appear from these studies that any solution injected into the prostate, whether it is physiologic solution of sodium chloride, distilled water or solution of a so-called antiseptic character, results in marked destruction of the acini, chronic inflammatory changes and marked fibrosis. The clinical benefit reported after this procedure might be attributed more properly to fibrotic replacement of infected glandular areas than to an immediate antiseptic effect at the time of injection.

(To be continued)

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ORIGIN OF FETAL ADENOMA IN THE THYROID GLAND

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The term "fetal adenoma" has long occupied a place in the literature on the thyroid gland. The first use of this term is generally credited to Wölfler,[1] who in 1883 used it to designate certain nodular tumors of the thyroid gland, which he thought arose from fetal cell rests. With an advance in knowledge, however, the concept of a fetal origin for these nodules has largely been discarded, although through usage the term persists in the literature. Today it has come to designate a distinctive type of nodule, on the general features of which most observers are agreed.

While a detailed description of a typical "fetal adenoma" will be given later (fig. 1), a few of its distinctive features may be cited here. Such a nodule is discrete, circumscribed, encapsulated and of variable size, occurring alone or multiply and presenting to the unaided eye a dull gray homogeneous substance with no evidence of lobulation. Histologically, it is comprised of small groups of cells, with or without acini, that may have a uniform distribution or show a tendency to congregate toward the periphery of the nodule. The acini are embedded in a homogeneous, eosinophilic, acellular matrix, not unlike colloid in its staining reactions, which is characteristically lacking in connective tissue. The nodule usually has a rich capillary blood supply.

Wölfler noted the occurrence of circumscribed areas in the thyroid gland "varying in size from that of the head of a pin to that of a goose egg." Variations in color and consistency were noted. Some glands contained more than one "adenoma." Microscopically, the smaller nodules were "formed of nonorganized gland cell tissue" and

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[1] Wölfler, A.: Ueber die Entwickelung und den Bau des Kropfes, Arch. f. klin. Chir. **29**:1-97, 1883.

"looked like the embryonic thyroid." In his material it was rare to find the "formation of large vesicles or extensive colloid degeneration." Without knowing the etiology and pathogenesis of an adenoma of the thyroid gland, he stated "with some sureness that they are of congenital nature," and more specifically, that they arise from interacinar cell rests. He further added that "these adenomas have a perceptible size at time of birth" or that "they develop at the time of puberty or pregnancy out of congenital structures."

Wölfler's concepts as recorded by his descriptions and diagrams have some features which suggest that he was dealing with nodules of different types and even with true benign neoplasms. Technical improvements in the microscopic examination of tissues, notably examination of whole glands and serial sections, have disclosed certain erroneous deductions in the investigations of earlier workers. The uncertainty of Wölfler's observations and their interpretation makes appraisal of his views impracticable. Nevertheless, he represents the school which originally sponsored the fetal origin of this condition.

Beck,[2] even earlier than Wölfler, attributed a fetal origin to adenomas of the thyroid gland. Ribbert[3] in 1915 resurrected the same belief. One cannot be certain, however, whether he had in mind the "fetal adenoma" exclusively or the comparatively rare true benign neoplasm, or even both types of lesions. While adhering to the fetal origin of the adenoma, he suggested a different mechanism for its formation. He described isolated cell groups in the form of solid epithelial bodies, lying between alveoli that did not possess lumens and were surrounded by a thin layer of connective tissue. Generally not more than two such bodies could be found in a single gland. Ribbert expressed the belief that these were not formed at puberty or when the adenoma first became visible, but that their occurrence must be attributed to rests of embryonal epithelium which did not form alveoli with lumens but continued to form solid cell masses. Thus, while Ribbert's description would indicate that he was considering a true benign neoplasm, his opinions, nevertheless, have become associated with those having to do with the so-called fetal adenoma and the embryonal origin thereof.

Virchow,[4] Hitzig[5] and Michaud[6] represent the school of earlier writers who explained the formation of an adenomatous nodule in the thyroid gland on a basis other than origin from fetal cell rests. Virchow, writing on pathologic tumors in 1863, discussed the process of hypertrophy and of hyperplasia and pointed out that each, at times, is a manifestation of normal growth. By a process of budding in certain parts of the follicles, he explained that small solid cones of cells push themselves into the interstitial tissues and, because of an increase in the latter, become isolated as discrete growths, which eventually acquire a fluid-containing lumen. This process, which he believed to be the fundamental one in the formation of goiter, may be diffuse or focal. He attributed the occurrence of an adenomatous nodule to secondary inflammatory changes.

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[2] Beck, B.: Ueber eingesackten Drüsengewebe-Kropf, Arch. f. physiol. Heilk. **8**:136-138, 1849.

[3] Ribbert, H.: Das Adenom der Schilddrüse, Frankfurt. Ztschr. f. Path. **18**: 55-56, 1915.

[4] Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 3, no. 1, pp. 15-17.

[5] Hitzig, T.: Beiträge zur Histologie und Histogenese der Struma, Arch. f. klin. Chir. **47**:464-502, 1894.

[6] Michaud, L.: Die Histogenese der Struma nodosa, Virchows Arch. f. path. Anat. **186**:423-477, 1906.

Hitzig expressed the belief that a nodular goiter begins as a single area of differentiated epithelium, which, by a process of metaplasia, gradually replaces the normal tissue of a lobule or even of a lobe. This process, he explained, is essentially due to a difference in the growth potential of neighboring parts of the gland.

Michaud summarized the beliefs of this group when he said: "We believe as Virchow that a goiter nodule develops out of normal epithelium, with Hitzig's modification that it is simply a substitution of normal thyroid tissue by changed cells which arise from the normal tissue."

In considering the present day concepts of the "fetal adenoma," we find less unanimity of opinion as to its nature than existed among the early writers. On only one point does there seem to be any general agreement, and that is that the lesion is not fetal in origin. While most writers recognize it as an interesting histologic entity, its pathogenesis has not generally been elaborated on. Some positive views have been expressed, which are given here.

Rienhoff and Lewis,[7] in their discussion of benign tumors, expressed the belief that the term "fetal adenoma" is a misnomer and should be discarded because of insufficient evidence to support the theory of origin from interacinar embryonal cell rests. However, in discussing the hyperplasia-involution cycle, they pointed out that certain glands may undergo an extreme degree of hyperinvolution and that this same type of extreme involutional change is also to be found in the so-called fetal and mixed adenoma.

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[7] Rienhoff, W. F., and Lewis, Dean: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16**:79-116 (Jan.) 1928. Rienhoff, W. F.: Involutional or Regressive Changes in Thyroid Gland in Exophthalmic Goiter, and Their Relation to Origin of So-Called Adenomas, ibid. **13**:391-425 (Sept.) 1926. Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1935.

Boyd[8] stated that many of the nodules which have been regarded as fetal in type are essentially only varieties of the colloid adenoma, since both may be seen shading into the other in the same sections. He noted further three special features about the "fetal adenoma," namely, (1) numerous thin-walled dilated vascular channels, (2) frequent extensive hemorrhages and (3) active budding of the acini within the adenoma. In addition there are a small number of adenomas which have the characteristics of a neoplasm and possibly arise from fetal cells. These are composed of strands of solid clusters of cells with no lumens, supported in a delicate vascular stroma.

MacCallum[9] rejected the term "fetal adenoma" and considered this lesion as a type of nodular goiter, arising from adult cells and frequently occurring in company with colloid nodules.

Wegelin[10] expressed the belief that the "fetal adenoma" arises in later life from thyroid tissue and is not fetal in origin.

Williamson and Pearse[11] stated that the fetal adenoma is a manifestation of a retrogressive phenomenon, attributable to perilobar fibrosis.

Hertzler[12] expressed the belief that the nodule begins as a mass of thyroid tissue which has never reached an adult stage and that it shows malignant tendencies and should be looked on as a true neoplasm.

Kline[13] cited evidence to support the belief that the development of all forms of adenomatous goiter depends essentially on an irregularity in the degree of proliferation of acini in different portions of the gland.

Else,[14] writing on "Adenomatosis or the Diffuse Adenomatous Goiter," described what he regarded as a clinicopathologic entity characterized by a diffuse new formation of acini, usually involving the entire thyroid gland. In the beginning the growth is of the fetal type without secretion, but later it progresses to the adult type; it does not give rise to symptoms at first, but later signs of hyperthyroidism appear. On studying the pathogenesis of this condition he found masses of undifferentiated cells, from which arose acini of the fetal type, followed in turn by the formation of a more adult type of colloid-secreting acinus. Different rates of development in various parts of the gland gave the nodular effect, and encapsulation was poor. As to the origin of these new acini, he favored the view that they arise from interstitial cells but also suggested that they may develop from the cells lining the old acini but growing "outside" the walls of these acini. Wilson[15] in 1913 described a similar condition and applied the term "adenomatosis." Goetsch[16] in 1920 described the early stage of this growth, applied the term "diffuse adenomatosis" and regarded the formation of acini as "an abortive attempt at the formation of young small alveoli."

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[8] Boyd, William: Surgical Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1933.

[9] MacCallum, W. G.: A Textbook of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

[10] Wegelin, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 1.

[11] Williamson, G. S., and Pearse, I. H.: The Pathological Classification of Goitre, J. Path. & Bact. **28**:361-387, 1925.

[12] Hertzler, A. E.: Mixed Tumors of Thyroid Gland (Fetal Adenomas), Arch. Surg. **16**:1187-1200 (June) 1928.

[13] Kline, B. S.: The Origin of Adenomatous Goiter, Am. J. Path. **1**:235-239, 1925.

[14] Else, J. E.: Adenomatosis, or the Diffuse Adenomatous Goiter, J. A. M. A. **85**:1878-1882 (Dec. 12) 1925.

Marine and Lenhart[17] regarded the "fetal adenoma" as a benign tumor which shows wide variations in its histologic picture, particularly in regard to the amount of colloid present and the height of the epithelium. They expressed the belief that it has a period of active growth and a resting period, comparable to physiologic hyperplasia, and, further, that iodine produces no change in the colloid.

HISTOLOGIC DESCRIPTION

The purpose of this paper is to show what we believe to be the origin of "fetal adenoma." This formation is identified by its specific histologic structure, and for clarity we have chosen a typical example for description (figs. 1 to 3).

Under low power magnification, section of such a growth shows a discrete, ovoid nodule, measuring about 4 cm. in its longest diameter and bordered by a thin capsule. This capsule is composed of strands of fibrous connective tissue, enmeshed in which are compressed thyroid follicles lined by atrophic epithelium. A few lymphocytes are present in the interstitial tissue. At irregular intervals the capsule sends fibrous strands into the substance of the nodule for short distances, usually accompanied by blood vessels. The central portion of the nodule is devoid of fibrous tissue.

The supporting framework is a loose reticulum, enmeshed in which is a pale, homogeneous, eosinophilic, acellular matrix. This material resembles intra-acinar colloid in sections stained with hematoxylin and eosin, and it displays the staining reaction of colloid in sections stained by Unna's method.

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[15] Wilson, L. B.: The Pathology of the Thyroid Gland in Exophthalmic Goiter, Am. J. M. Sc. **146**:781-790, 1913.

[16] Goetsch, E.: Disorders of the Thyroid Gland, Endocrinology **4**:389-402, 1920.

[17] Marine, D., and Lenhart, C. H.: The Pathological Anatomy of the Human Thyroid Gland, Arch. Int. Med. **7**:506-536 (April) 1911.

The follicles are most abundant at the periphery, and the adjacent capsule is intimately attached. Toward the center of the nodule the follicles become less numerous but otherwise appear to be similar to those at the periphery. The follicles are uniformly small and round and contain little or no colloid; when present, the colloid is pale and vacuolated. The individual cells are uniformly large and high cuboidal and contain abundant cytoplasm, in which granules and vacuoles are seen. The nuclei are large and deeply basophilic, and many show one or more nucleoli. Histologically, these cells appear to be active. In the central, less dense areas, the follicles assume a chainlike configuration, with from three to eight small follicles lying in a row. In some of these chains a contiguous lumen may be detected. This suggests the formation of new follicles by a process of budding, similar to that which is known to occur in the development of the fetal thyroid. This same chainlike configuration is seen near the periphery, but it is not as apparent there as in the less dense areas.

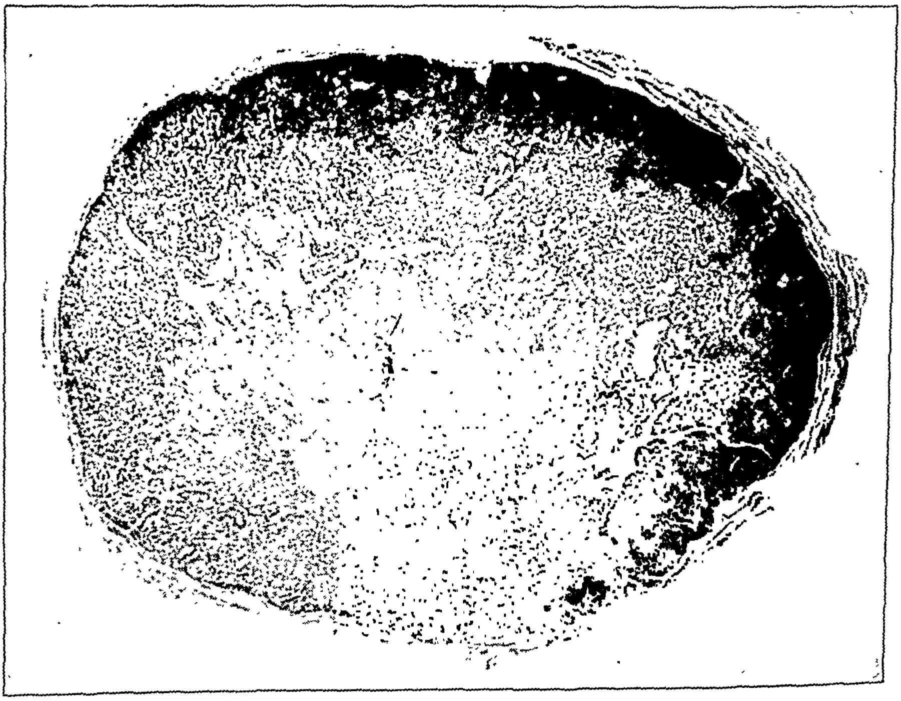


Fig. 1.—Low power photomicrograph of a typical fetal adenoma. Note the capsule and the peripheral concentration of acini.

The nodule is well vascularized throughout. In the capsule, numerous large blood vessels are seen entering the periphery of the nodule. At these points there is a moderate amount of perivascular connective tissue, which appears to be carried in from the capsule. Within the nodule the tissue is even more richly vascularized, the vessels appearing

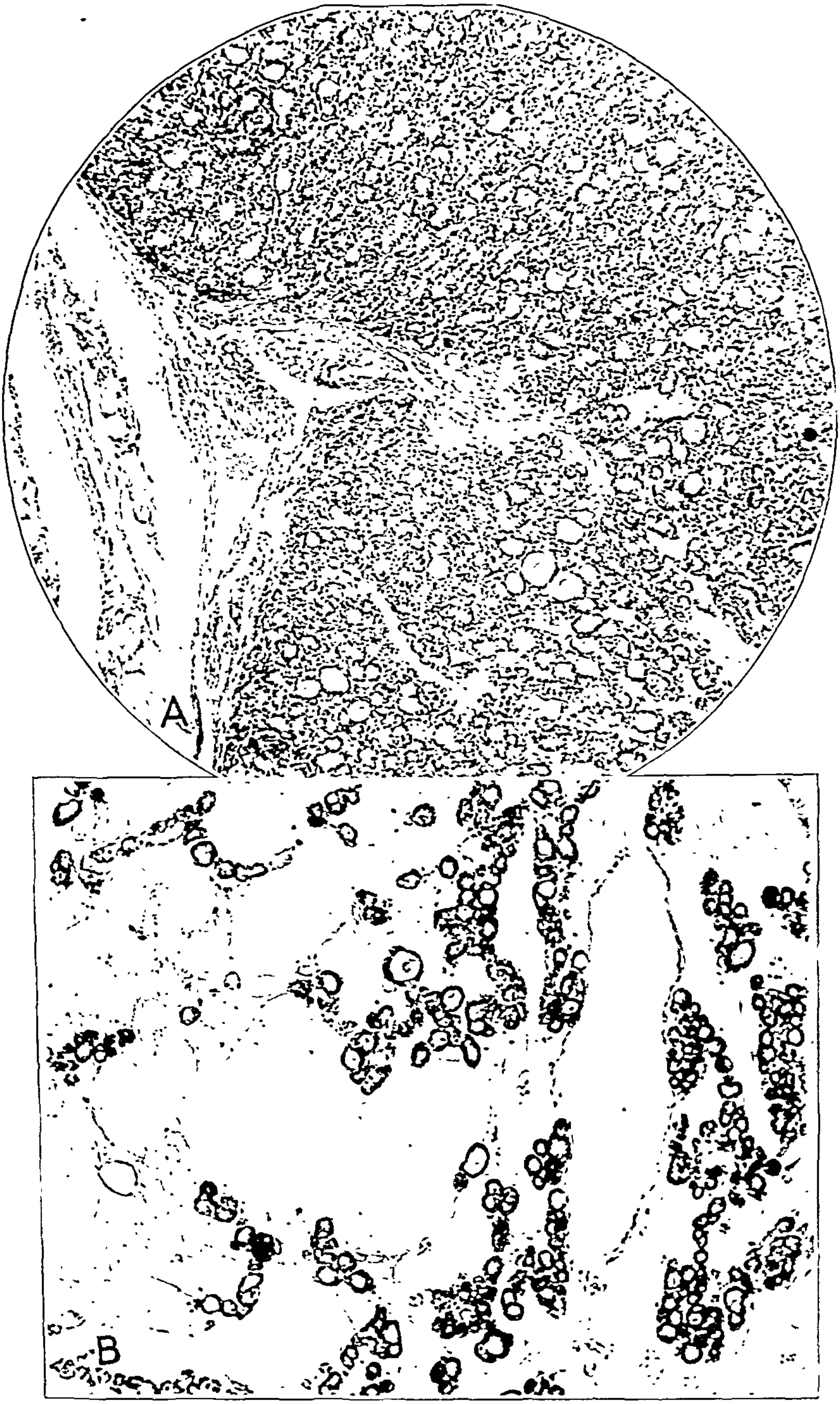
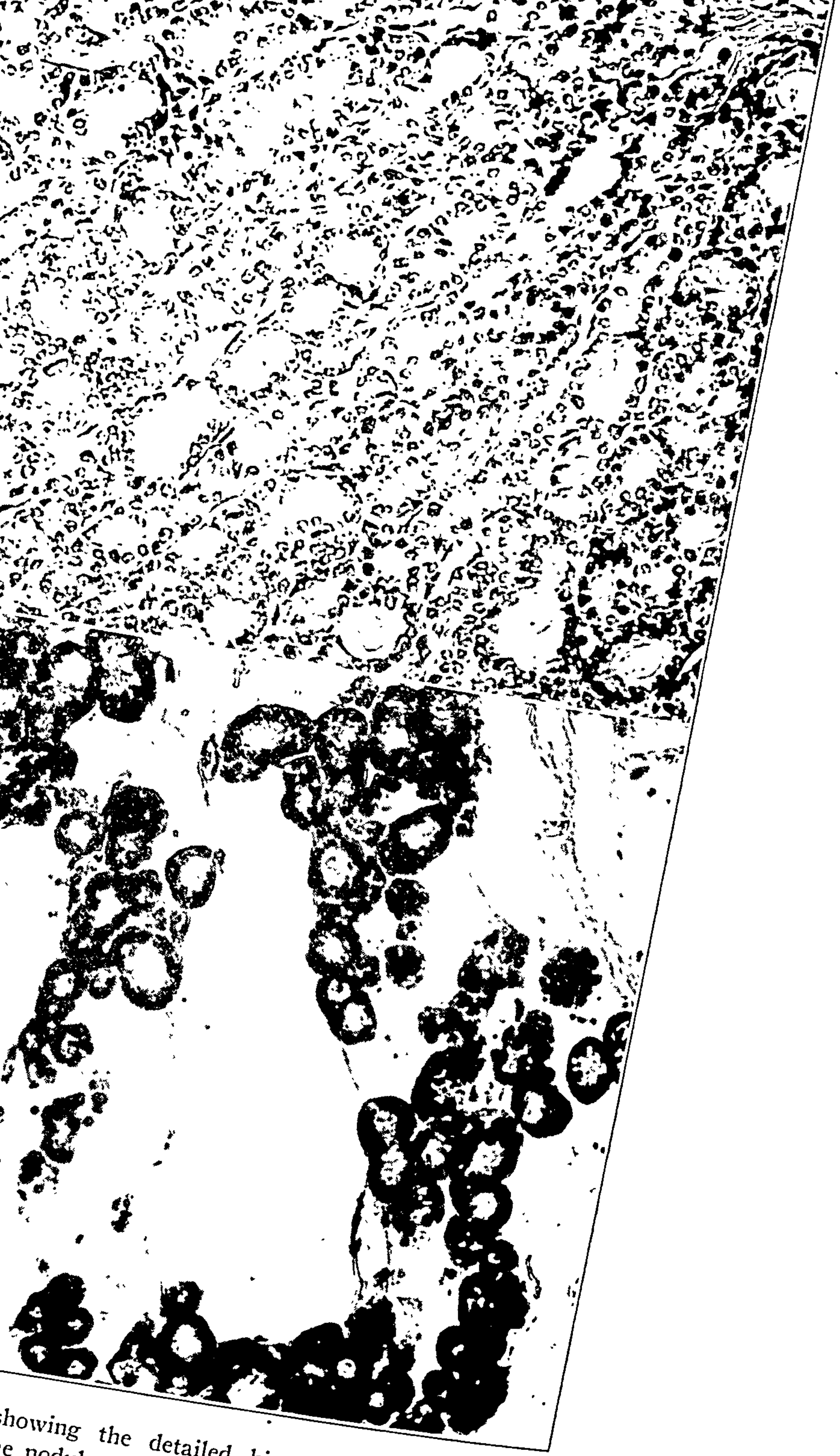


Fig. 2.—Medium power photomicrographs of the fetal adenoma in figure 1, showing the periphery and the central portion of the nodule. Note the dilated endothelium-bound spaces in the center.



howing the detailed histologic structure at the e nodule. Note that the epithelium in the center e periphery.

merely as endothelium-lined spaces lying adjacent to closely packed acini. Near the center these vessels become markedly dilated and possess little or no supporting tissue.

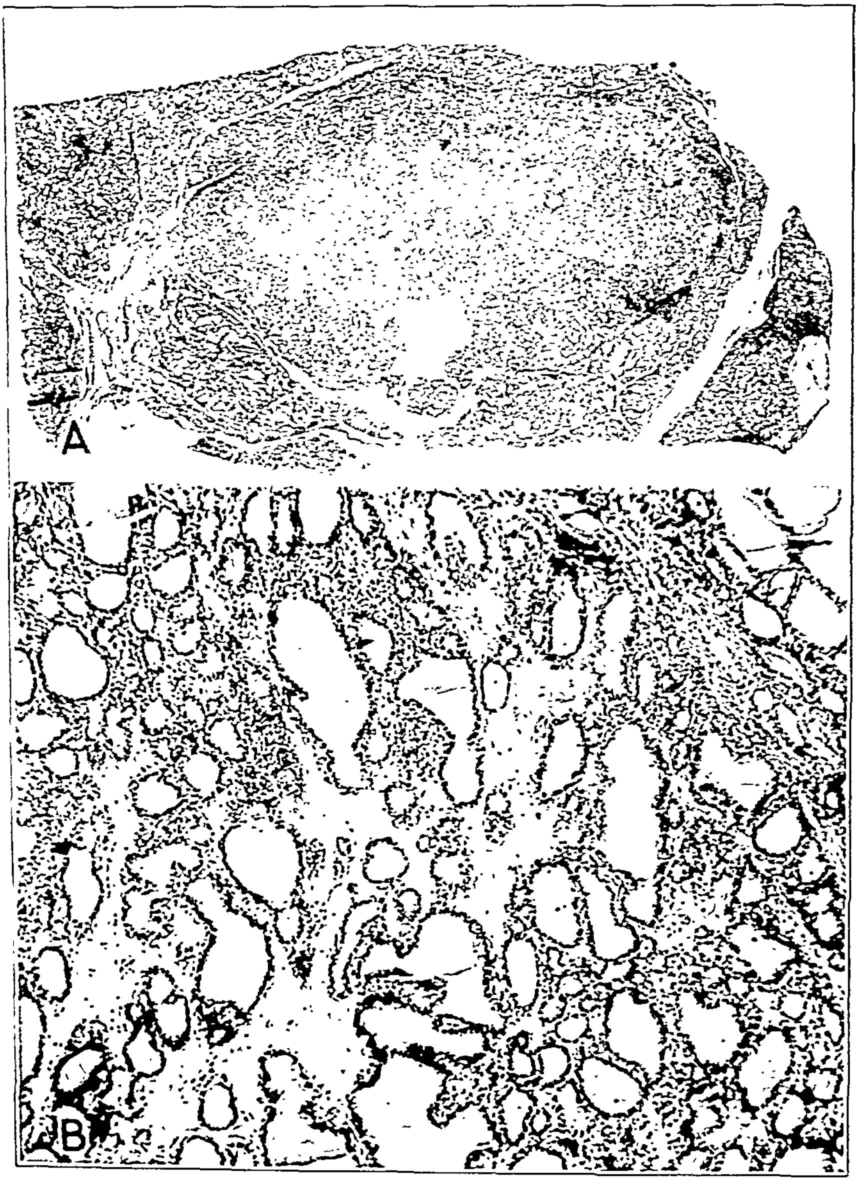


Fig. 4.—*A*, section of a fetal adenoma showing the peripheral acini undergoing hyperplasia and colloid deposition. *B*, high power magnification of the peripheral zone shown in *A*.

Noteworthy features in the foregoing description are (figs. 1 and 3): (1) small acini composed of normal adult thyroid cells; (2) absence of supporting connective tissue; (3) presence of numerous large endothelium-lined spaces, and (4) an acellular colloid-like matrix.

The individual components, acini, blood vessels and interacinar tissue, in this lesion are not characteristic of this particular nodule. It is rather the peculiar pattern they assume which gives the characteristic picture.

We have frequently seen nodules which present the typical appearance of a "fetal adenoma" near the center, while at the periphery they show larger acini composed of normal thyroid cells which are filled with colloid. In some instances these acini undergo hyperplasia, apparently reacting similarly to the remainder of the gland (fig. 4). On the other hand, we have seen this same picture as focal areas in a non-nodular gland. These changes have been repeatedly observed in routine autopsy material as well as in surgical specimens.

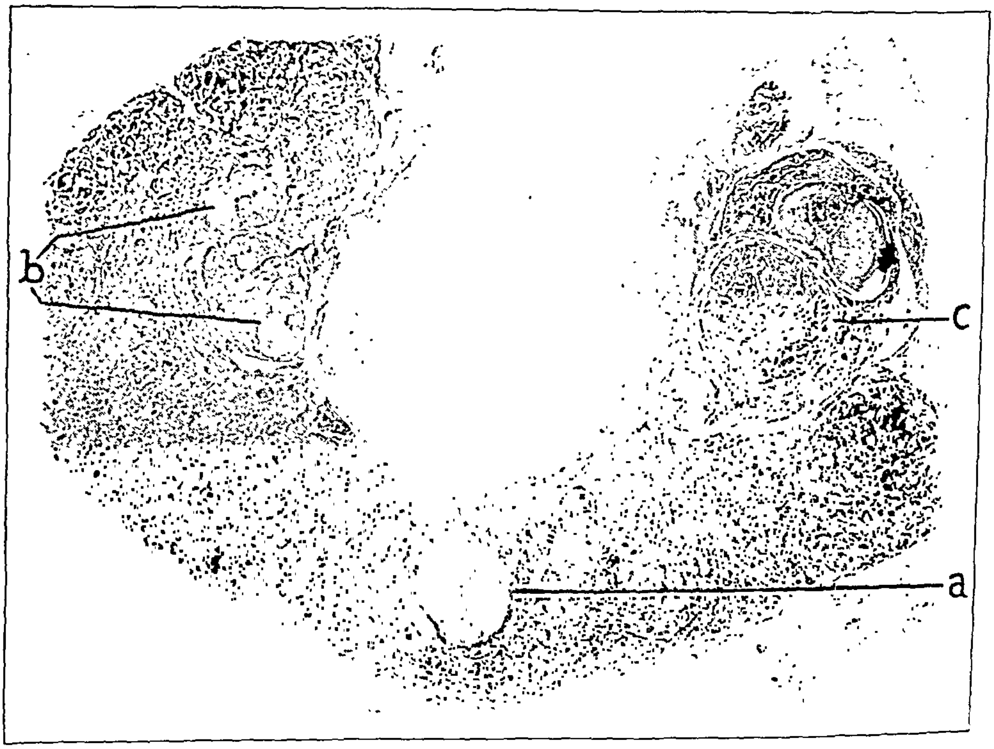


Fig. 5.—A transverse section through the whole gland, showing (*a*) a colloid body, (*b*) several colloid bodies into which papilliferous hyperplasia is taking place and (*c*) a nodule presenting the fetal pattern.

The "fetal adenoma" appears to consist of active thyroid cells, capable of undergoing the same histologic changes as those in a normal gland. We believe that the arrangement of the acini and not the acinus is the typical feature of the "fetal adenoma." This arrangement we have termed the "fetal pattern." The next step is to show the method of formation of this pattern.

Figure 5 shows a transverse section through both lobes and the isthmus of a thyroid gland removed at autopsy from a 29 year old Negress, who was seven months pregnant, had a 4+ Wassermann reaction and after intravenous injection of thiobismuth collapsed and died in twenty-four hours. There were no apparent signs of hyperthyroidism.

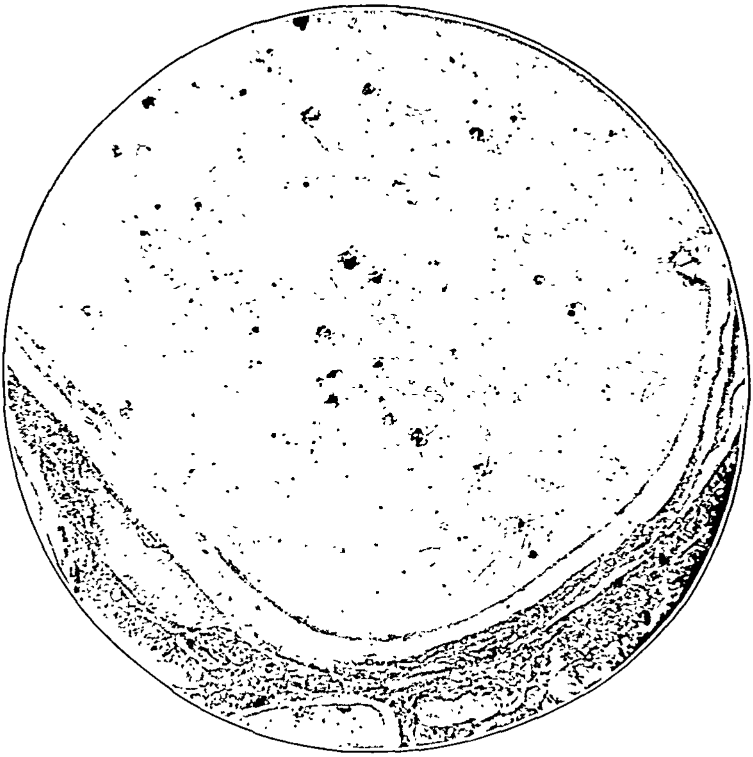


Fig. 6.—High power magnification of the colloid body in figure 5.

On macroscopic examination of the gland on section, about six or eight discrete areas were seen scattered through the gland, giving it a nodular appearance. Microscopically, these areas may be classified in three groups, namely, (*a*) a single large colloid body, (*b*) several colloid bodies within which a papilliferous type of hyperplasia was taking place and (*c*) a large nodule which was almost completely filled by hyperplastic epithelium. The remainder of the gland showed a normal lobular configuration together with manifestations of diffuse hyperplasia.

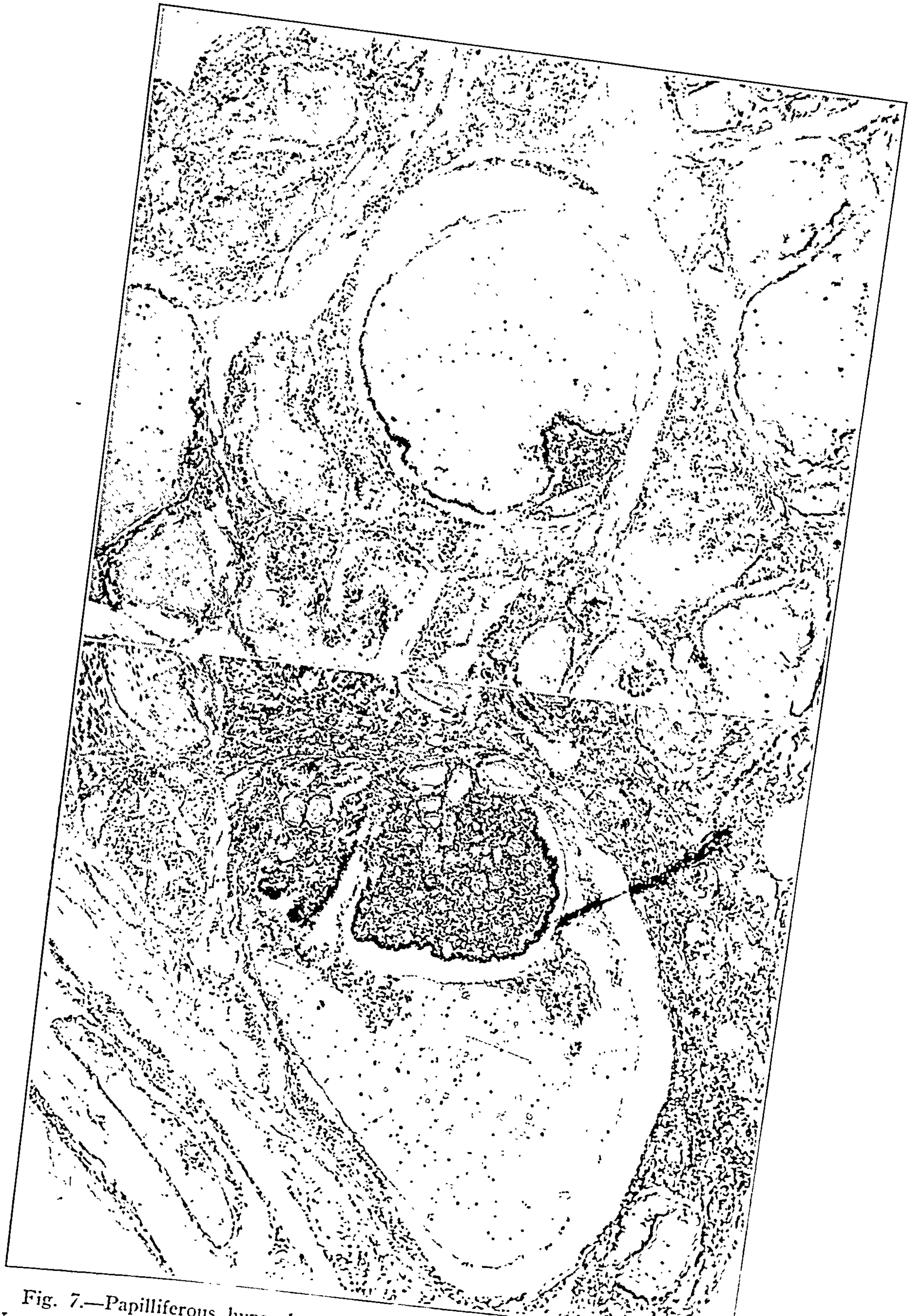


Fig. 7.—Papilliferous hyperplasia into the colloid bodies shown in figure 5*b*. Note the progressive stages of development as shown in these sections and in those in figure 8.

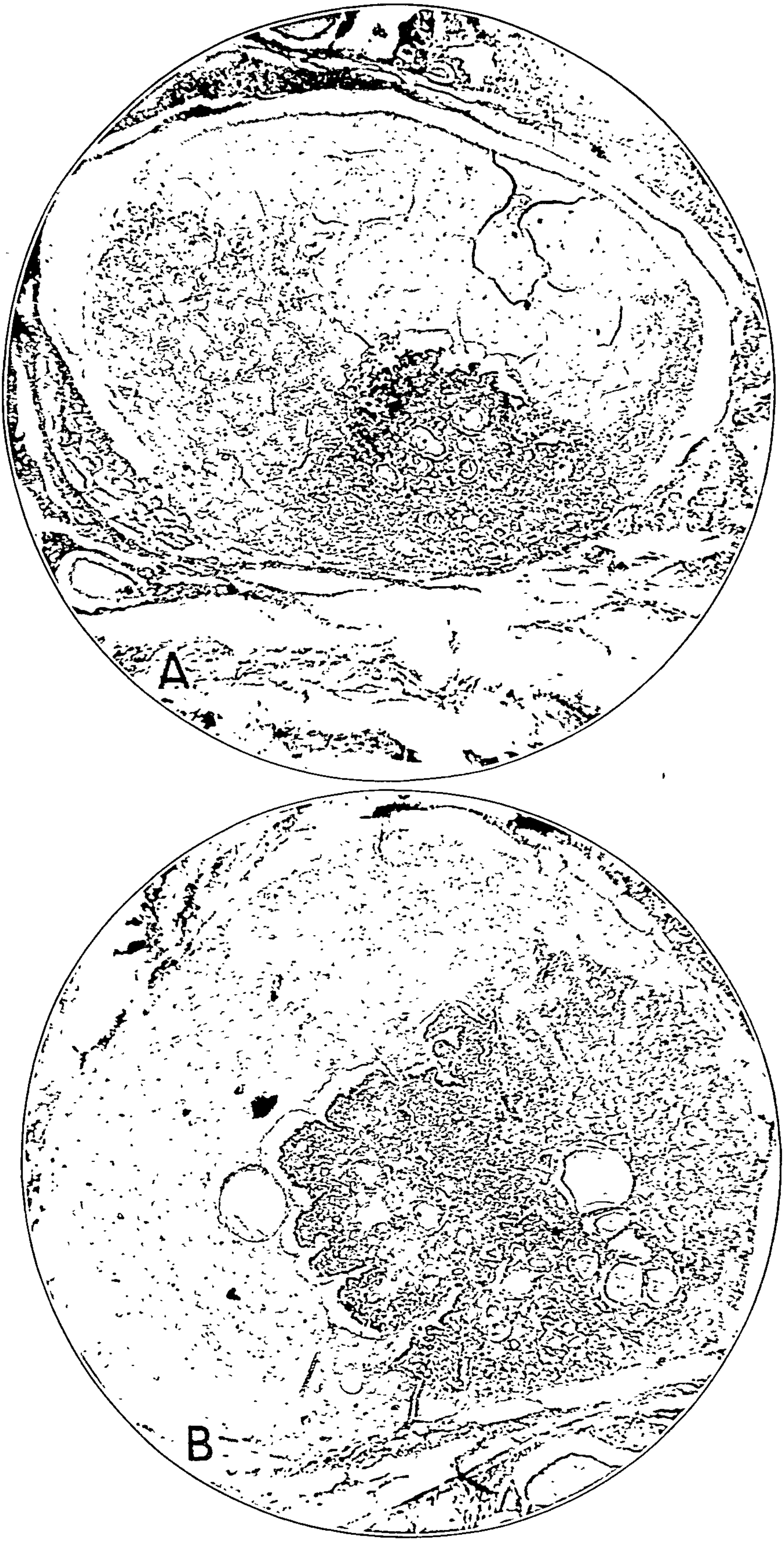


Fig. 8.—Further stages of papilliferous hyperplasia into the colloid bodies.

The single large colloid body (fig. 6), the position of which is shown in figure 5 *a*, was about 0.5 cm. in diameter. It was filled with deep-staining homogeneous colloid. The lining was composed of a single row of flattened epithelium. A pseudocapsule composed of a few loose strands of connective tissue surrounded the follicle.

The colloid bodies in the second group (figs. 7, 8 and 9) varied in size from 0.2 to 0.5 cm. in diameter and were filled with deep-staining, nonvacuolated colloid. One side of the follicle was lined by compressed, flattened epithelium, while at the opposite side the epithelium was hyperplastic, manifesting itself as a papilliferous type of growth composed of finger-like and clublike projections into the colloid (fig. 9). As this tortuous epithelial wall advanced, it left behind it a matrix of colloid in which were formed numerous small follicles lined with hyperplastic epithelium, which were seen in all stages of development, as they were "pinched" or "budded" by a process of invagination of the epithelial lining. These cells were large and high cuboidal and

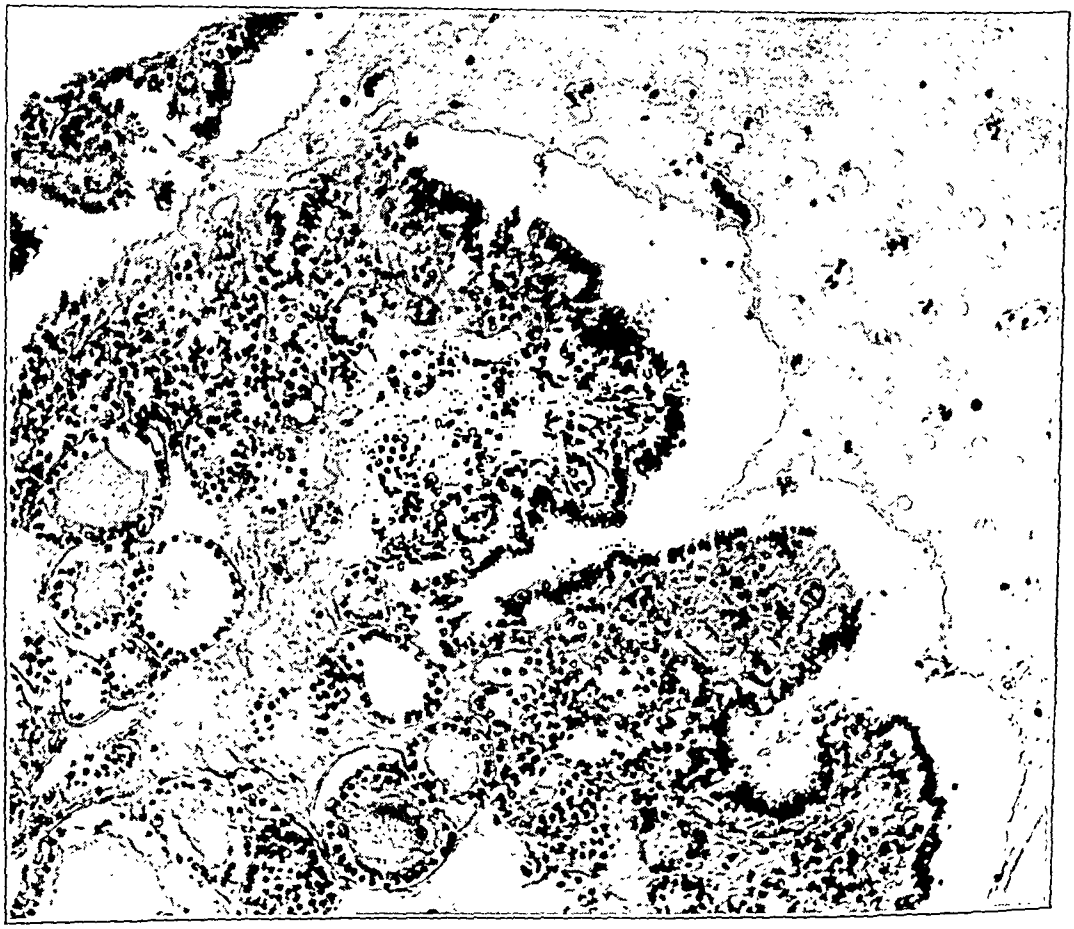


Fig. 9.—High power magnification of the section in figure 8 *B*, showing the typical fetal pattern.

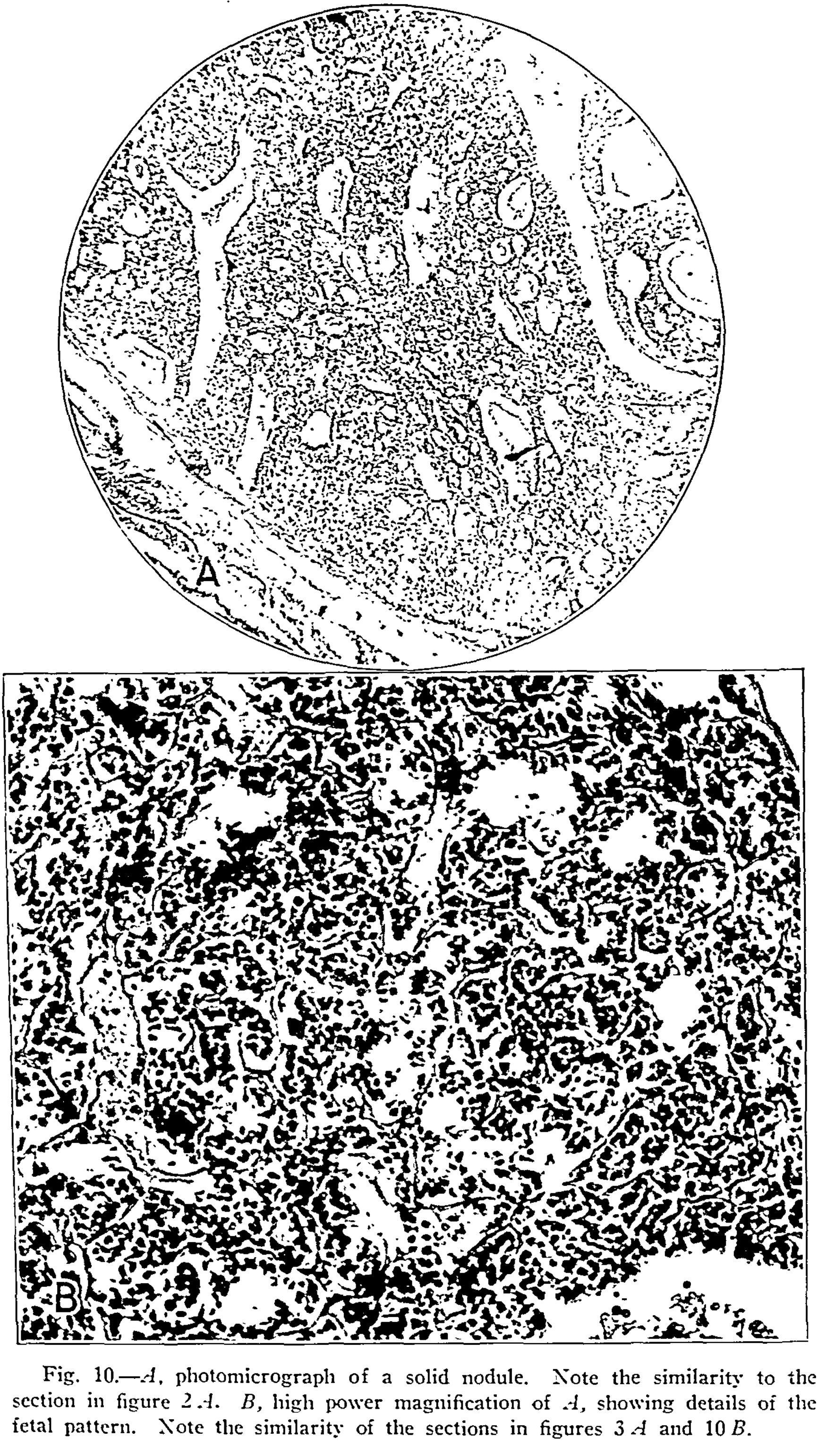


Fig. 10.—*A*, photomicrograph of a solid nodule. Note the similarity to the section in figure 2 *A*. *B*, high power magnification of *A*, showing details of the fetal pattern. Note the similarity of the sections in figures 3 *A* and 10 *B*.

contained abundant pale cytoplasm and large deeply staining granular nuclei. These hyperplastic areas were well vascularized. Numerous engorged vessels lying in close association with the follicles were present. In places, these blood channels might be seen invading the colloid itself. Figures 7 and 8 show the lesion in progressive stages of development in different nodules in the same section.

The large, apparently solid nodule (fig. 5 *c* and fig. 10) was about 1 cm. in diameter. It was surrounded by a narrow zone of loose connective tissue. Its structure was essentially the same as that of the hyperplastic zone found in the colloid bodies just described, the only noteworthy difference being that here no colloid was present, the entire nodule consisting of small hyperplastic follicles. The character of the epithelium was identical with that previously described, and the same degree of vascularization was present (fig. 10 *B*). This nodule presented the typical fetal pattern described in figure 3 *A*.

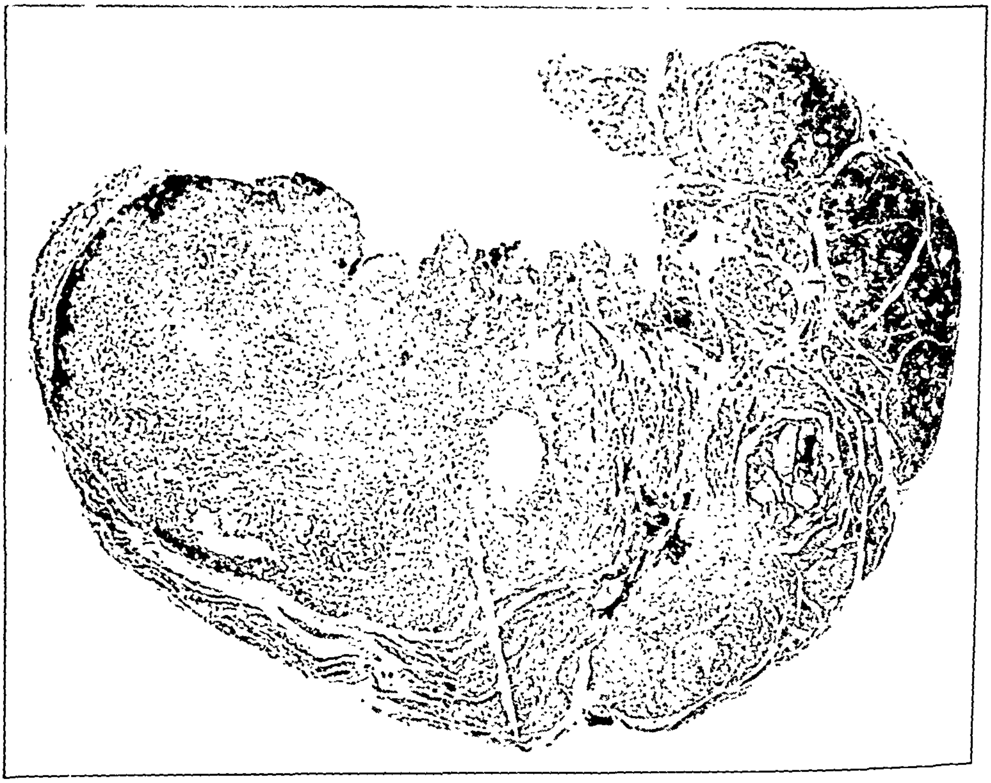


Fig. 11.—A large section through the entire lobe of a thyroid gland, showing a nodule of the fetal type.

The remainder of the gland showed evidence of hyperplasia of the intravesicular type.

We believe that the nodules described were originally colloid bodies. Hyperplasia of the epithelium occurred throughout the gland (a case of pregnancy), and the epithelial lining of the nodules became hyper-

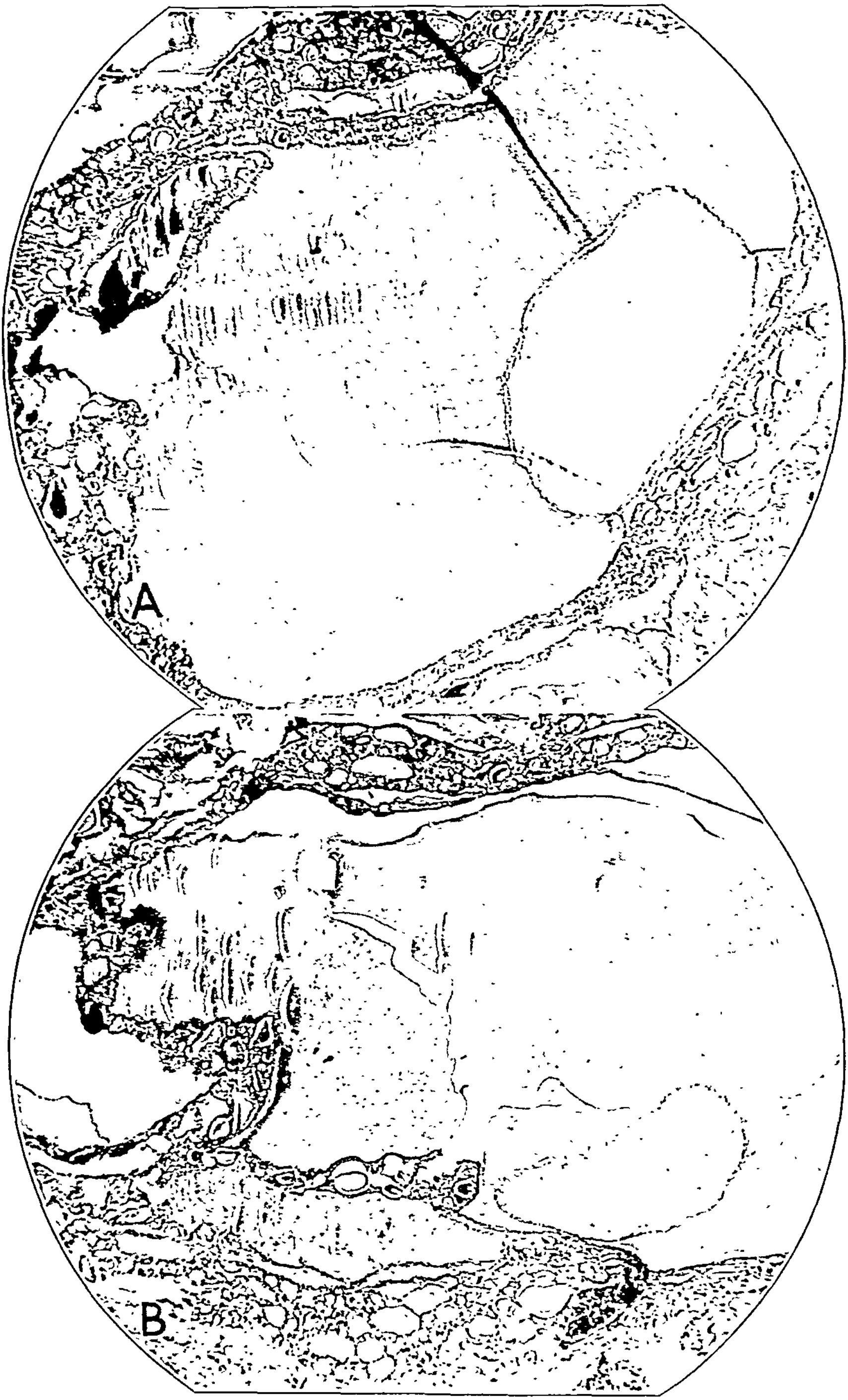


Fig. 12.—Section through the colloid body showing beginning hyperplasia at one border. Figures 12 to 15 are serial sections taken at 100 micron intervals through the same lesion.

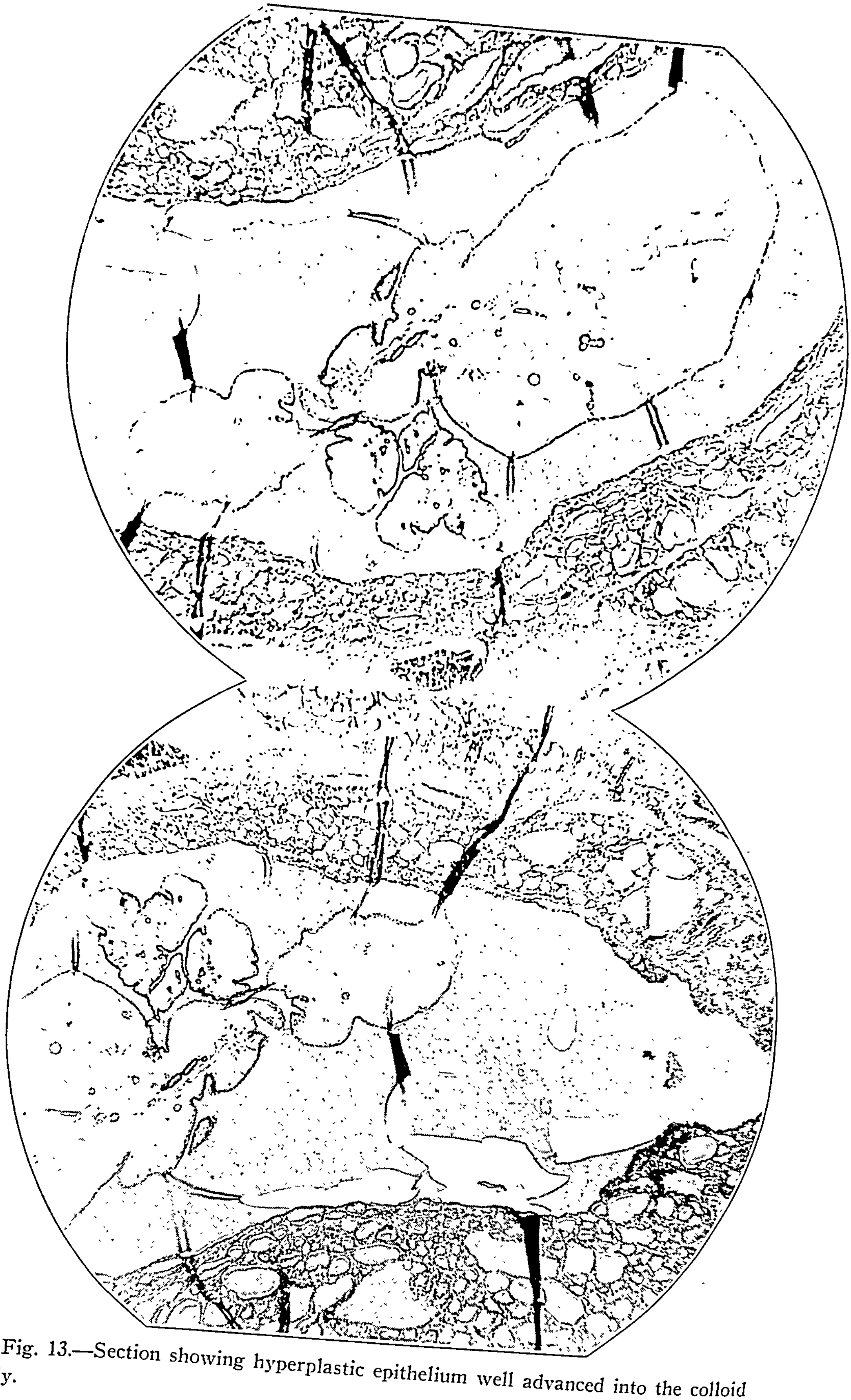


Fig. 13.—Section showing hyperplastic epithelium well advanced into the colloid body.

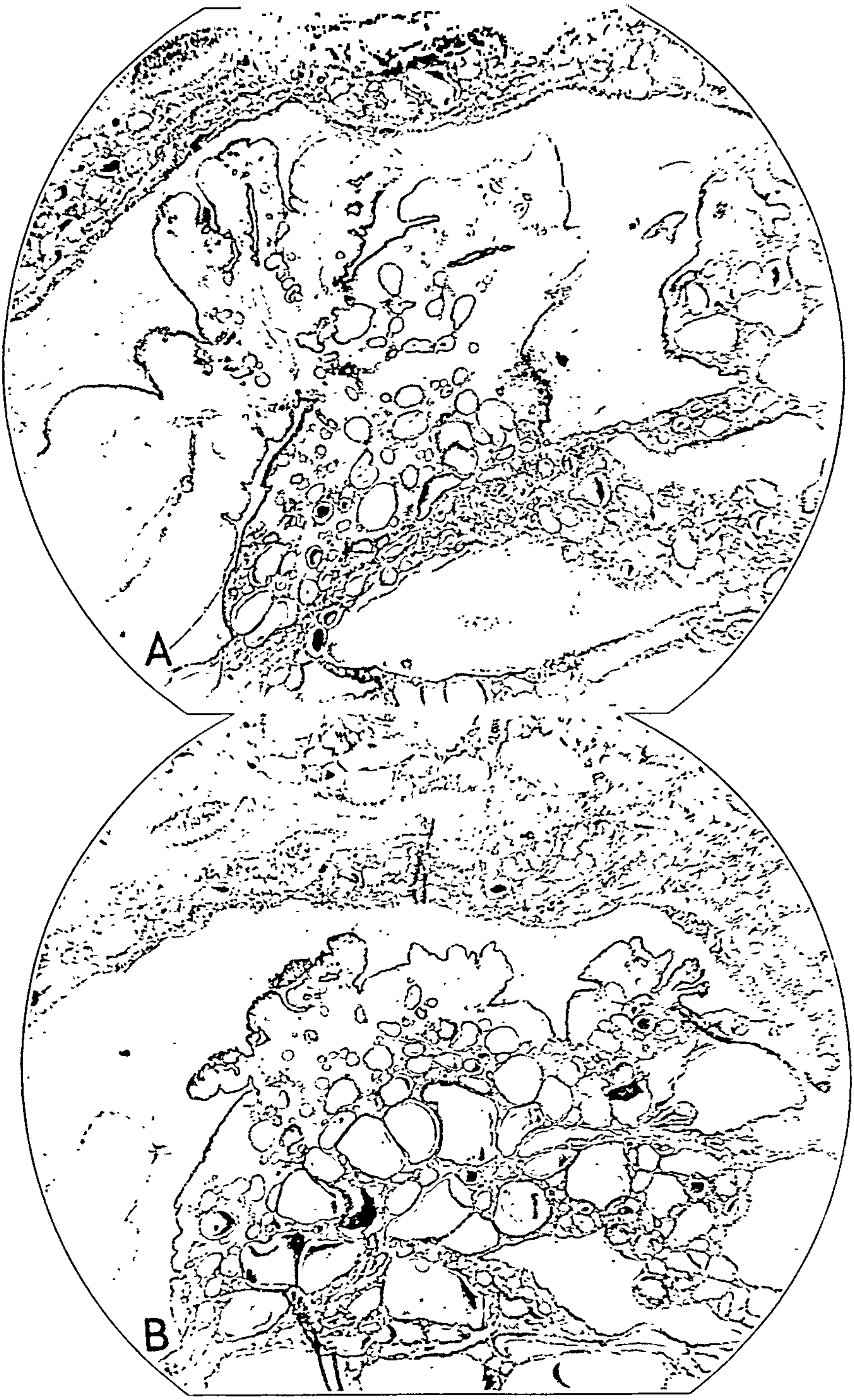


Fig. 14.—Further stages in the papilliferous ingrowth.

plastic, growing into the colloid. Three stages in the process were evident: (1) an unaltered colloid nodule, (2) the projection of hyperplastic epithelium into the colloid and (3) finally, complete replacement of the colloid by hyperplastic epithelial acini, arranged in the typical fetal pattern. In our routine surgical material this process has been frequently observed both in nodular and in non-nodular glands.

Figure 11 shows a section through the entire lobe of a gland, removed surgically, which to the naked eye presented the features of a nodular goiter containing one large and one small nodule. A large section was made, and the remainder of the gland was cut serially. Section through the larger nodule revealed that it was a fetal adenoma, similar in all essential features to the growth described in figure 1. The small nodule showed a focal area of hyperplastic epithelium, which had undergone moderate involution. The remainder of the gland showed evidence of a residual hyperplasia of a similar type.

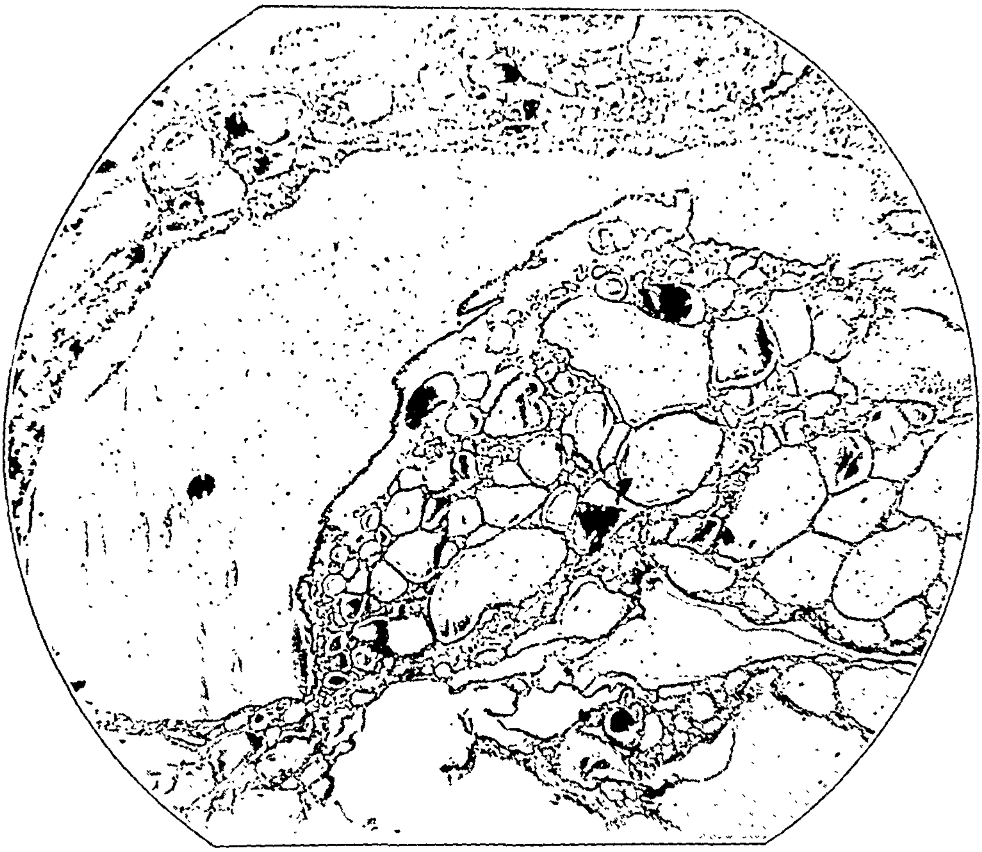


Fig. 15.—Section taken through the colloid body beyond the papilliferous ingrowth.

Serial sections through non-nodular portions of the gland revealed processes similar to those just described (figs. 12, 13, 14 and 15).

Taking a section at random, for example, that shown in figure 14 *B*, there was to be seen a large irregular colloid body filled with vacuolated colloid. On one side there was a border of flattened epithelium, while on the other side the epithelium was high cuboidal and hyperplastic, causing the outline of the colloid to be irregular, owing to the finger-like and clublike projections which the advancing wall of hyperplastic epithelium sent into the colloid. In the wake of or behind this epithelial wall there was a matrix of pale, eosinophilic, acellular material in which were found numerous small follicles lined with hypertrophic epithelium and containing deep-staining colloid. Some of these follicles could be seen in the process of formation, as they were "pinched" or "budded" off from the epithelium. This area was well vascularized, numerous small vessels lying in close relationship to the epithelium of the follicles. By serial section the lesion was seen to be a colloid body (fig. 12 *A*) in which a papilliferous type of hyperplasia had occurred (figs. 12 *B* to 16), partially replacing the colloid and reproducing the fetal pattern. Similar areas were noted elsewhere throughout the gland.

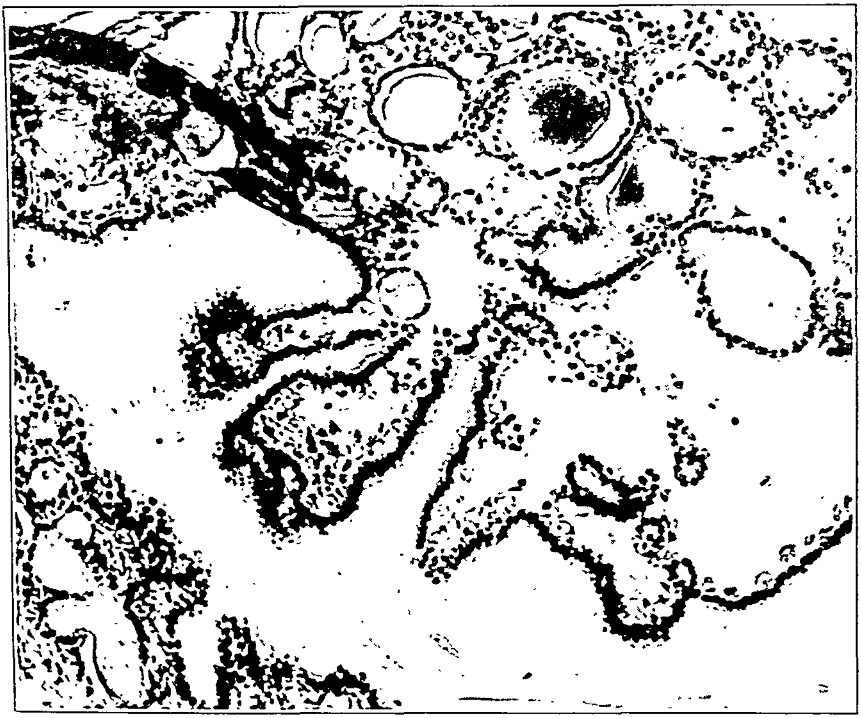


Fig. 16.—High power magnification of figure 14 *B*, showing marked hyperplasia with new acini in the process of formation.

In this type of hyperplasia the epithelium carries its blood supply with it, but in this variety of growth apparently the reaction occurs within an epithelium-lined space, and because the colloid gives temporary support to the invading epithelium, no proliferation of fibrous tissue occurs.

The appearance of the nodule depends on the size and on the secondary changes which may occur in it. If the original nodule is small, complete replacement by closely packed acini occurs (fig. 10 *A*), whereas in the larger lesions the replacement is incomplete, the acini being aggregated near the periphery close to the parent epithelium and widely scattered toward the center (fig. 1). As the colloid which originally supported the acini and blood vessels disappears, the capillaries dilate and rupture with resultant hemorrhage. Once hemorrhage has occurred, the initial picture is altered, and secondary changes, such as necrosis, cyst formation, scarring, hyalinization and calcification, may ensue, serving to alter or completely destroy the appearance of the initial nodule.

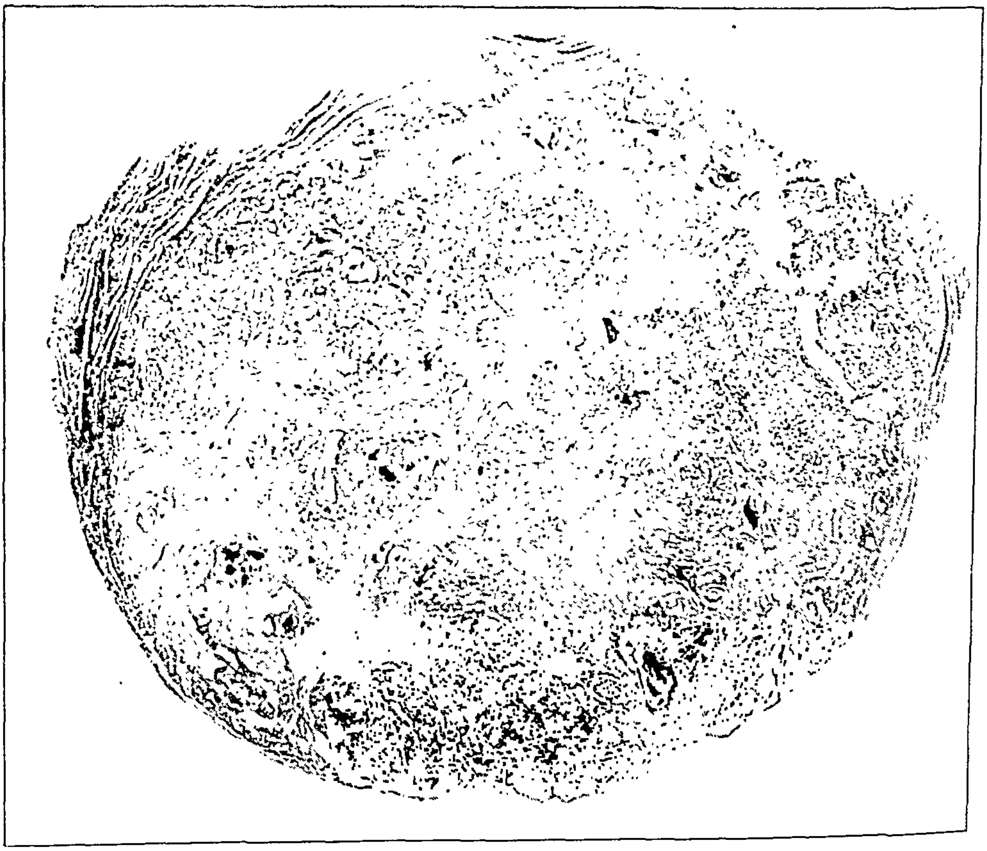


Fig. 17.—Low power magnification of a fetal nodule, showing marked secondary changes of hemorrhage cyst formation and scarring.

In the material examined, we were unable to trace any relationship between growth and carcinoma. However, in going over our material, Dr. Douglas Symmers suggested that the mode of origin herein demonstrated tends to support the belief that this type of lesion is sometimes prone to develop carcinoma because, although the new hyperplastic acini may become normally functioning thyroid epithelium, the abnormal method of their development may become still further diverted.

CONCLUSIONS

1. The nodule known as "fetal adenoma" is composed of regenerating thyroid epithelium, occurring in a colloid follicle or body.

2. This follicle may be small or large and encapsulated or non-encapsulated.

3. The peculiar appearance is due to the fact that the proliferation of epithelium occurs into the colloid, which supports the growth, eliminating the immediate necessity of fibrous supporting tissue.

4. In the larger nodules, as the colloid disappears the acini are left without apparent supporting tissue, except for the capillaries, which may become markedly dilated, thus giving rise to the peculiar appearance of the central portion of these growths.

5. Once the lesion is fully formed, there are four possibilities:

(*a*) The acini may function as normal thyroid epithelium.

(*b*) They may undergo hyperplasia, forming the nodular hyperplastic goiter, or so-called toxic adenoma.

(*c*) They may become carcinomatous.

(*d*) Hemorrhage may occur into the nodule followed by secondary degenerative changes, such as necrosis, cyst formation and fibrosis.

EXPERIMENTAL JOINT SPRAIN

PATHOLOGIC STUDY

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AND
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In a previous communication [1] the pathologic changes which followed the production of mild sprain in the knee joint of the rabbit were reported. Since that time, other similar experiments have been performed which are of greater interest, particularly since the results suggest the pathologic basis for the clinical condition termed chronic traumatic arthritis. As a foundation for the discussion, a résumé of the results in the most recent group of experiments together with those reported [2] previously is given.

METHOD

After varying amounts of manual force were applied to the knee and ankle joints of ten rabbits, a method was developed for the production of mild and severe forms of sprain without roentgenographic evidence of fracture.

In this manner, mild sprains were produced in twelve rabbits (group 1) and severe sprains in eleven (group 2). Roentgenograms of all sprained joints were taken immediately thereafter, and no evidence of injury to the bone was demonstrated. Autopsy was performed on the animals in group 1 in from one to six weeks after production of the sprain and on those in group 2 in from one to eleven weeks later. The joints were removed, roentgenograms were again taken and the specimens were examined grossly and microscopically.

Mild and severe sprains were produced in the same manner in a third group of twelve rabbits, and the sprained knee joints were immobilized in plaster of paris casts. Attempts were made to determine the effects of immobilization on the rate of healing, but since it was difficult to maintain satisfactory immobilization, the results were discarded.

RESULTS

Pathologic Changes After Mild Sprain (Group 1).—One week after mild sprain there was definite swelling of the joints. The synovial

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From the Division of Orthopedic Surgery, Department of Surgery and the Department of Pathology, Peiping Union Medical College.

[1] Miltner, Leo J., and Hu, C. H.: Experimental Reproduction of Joint Sprain, Proc. Soc. Exper. Biol. & Med. **30**:883, 1933.

[2] Miltner, Leo J.; Hu, C. H., and Fang, H. C.: The Pathology and Treatment of Joint Sprain, Chinese M. J. **49**:521, 1935. Miltner and Hu.[1]

membrane was edematous and had small foci of hemorrhage (fig. 1) and a few dilated blood vessels near its surface. The joint fluid was increased in amount and was more viscous and yellower than normal. There was slight pannus formation at the osteocartilaginous junctions on the injured side. The subcutaneous tissue and the loose connective tissue of the mesotendons showed evidence of hemorrhage. There was no blood within any of the tendon sheaths. Microscopic sections showed hemorrhage into and under the synovial membrane. The synovial cells showed marked vacuolation. The subsynovial tissue was edematous, with capillary congestion, early fibroblastic proliferation and considerable infiltration with leukocytes and lymphoid cells. In places the surface of the synovial membrane was covered with fibrin, while in others the fibrin was seen in the subsynovial tissues. Near the attachments to the bone, the injured capsule and ligaments showed similar changes consisting of edema, fibroblastic proliferation and infiltration with lymphoid cells. The loose connective tissue beneath the synovial lining of the tendon sheaths presented a picture essentially the same as that seen in the synovia.

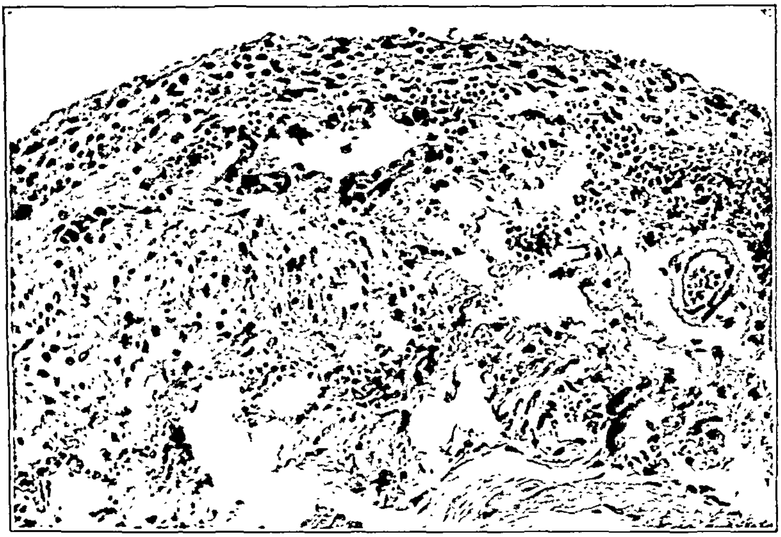

Fig. 1.—Photomicrograph (× 200) of the synovial membrane of a joint one week after mild sprain. Note the edema and foci of hemorrhage and early proliferation of fibroblasts in the loose subsynovial connective tissue. Other sections in the same area show infiltration with leukocytes and lymphoid cells.

Two and three weeks after the sprain there were still definite signs of acute inflammation of the synovial tissue. There was a great increase in the number of fibroblasts in the subsynovial tissue. Hemosiderin was found in large amounts in the phagocytic cells of the inflamed area.

At this stage hyalinized masses of fibrin were seen within the synovial tissue and on the synovial surface (fig. 2). The tendon sheaths and the soft tissue surrounding the capsule and ligaments showed changes similar to those which were found after one week, except that there was more marked fibroblastic proliferation.

After four weeks, there was no external evidence of swelling or other signs of old injury. Microscopic examination of the tendon sheaths, synovial tissue and ligaments still showed evidence of old hemorrhage. The number of fibroblasts was decreased, but the number of collagen fibers was increased. Many small capillaries were seen in this young connective tissue. In certain places the synovial membrane showed small foci of necrosis, with deposits of fibrin on the surface. There was still an appreciable amount of edema of the loose connective tissue, but the infiltration with leukocytes and lymphoid cells was much less than that shown in the sections taken after three weeks.

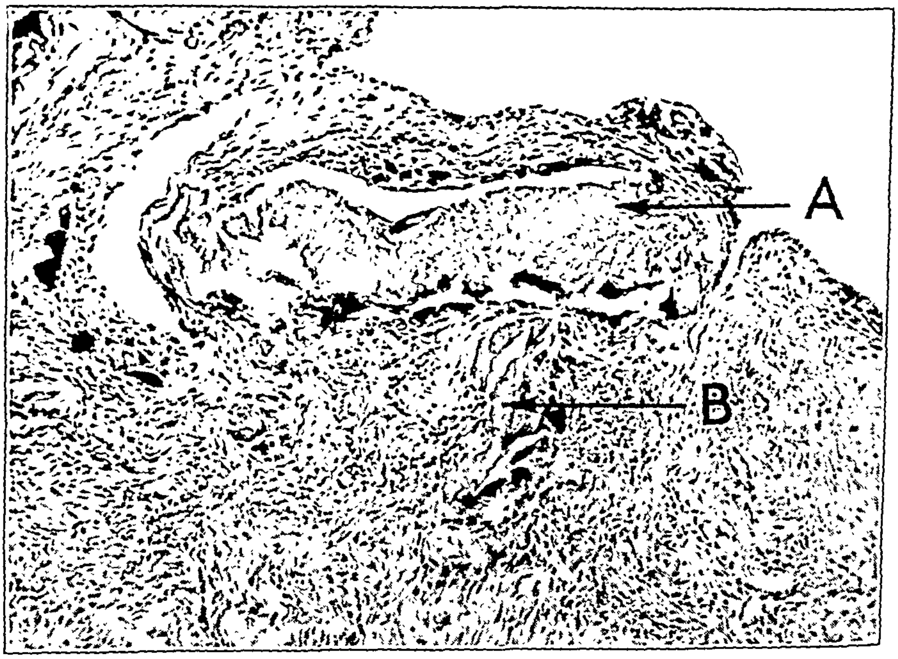

Fig. 2.—Photomicrograph (× 180) of the synovial membrane of a joint three weeks after mild sprain. Note the hyalinized mass of fibrin (*A*) between the villi and (*B*) within the subsynovial connective tissue.

Microscopic examination at six weeks showed complete healing of the traumatized parts. There was a late stage of fibrosis, with shrinkage and contraction of the connective tissue structures.

Pathologic Changes After Severe Sprain (Group 2).—In addition to the changes just described (after mild sprain), the joints subjected to severe sprain showed the following pathologic changes: A fibrillar degeneration of the surface layers of the cartilage was seen, especially at the margins of the joint surfaces on the affected side. New fibroblasts, apparently arising from the synovial membrane, had already attached themselves over these areas of cartilage as early as the second week. The inner free portion of the semilunar (fibrous) cartilage on the affected side showed slight necrotic changes. After six weeks, the distal free ends of the semilunar cartilage showed a more advanced stage of the fibrillation with exfoliation of the superficial layers and hyalinization of the deeper layers of cells. At the end of the eighth and tenth weeks, several specimens showed complete degeneration of the free portion of the semilunar cartilage. In all the specimens the intra-articular cartilage of the tibia on the side of the joint opposite to the

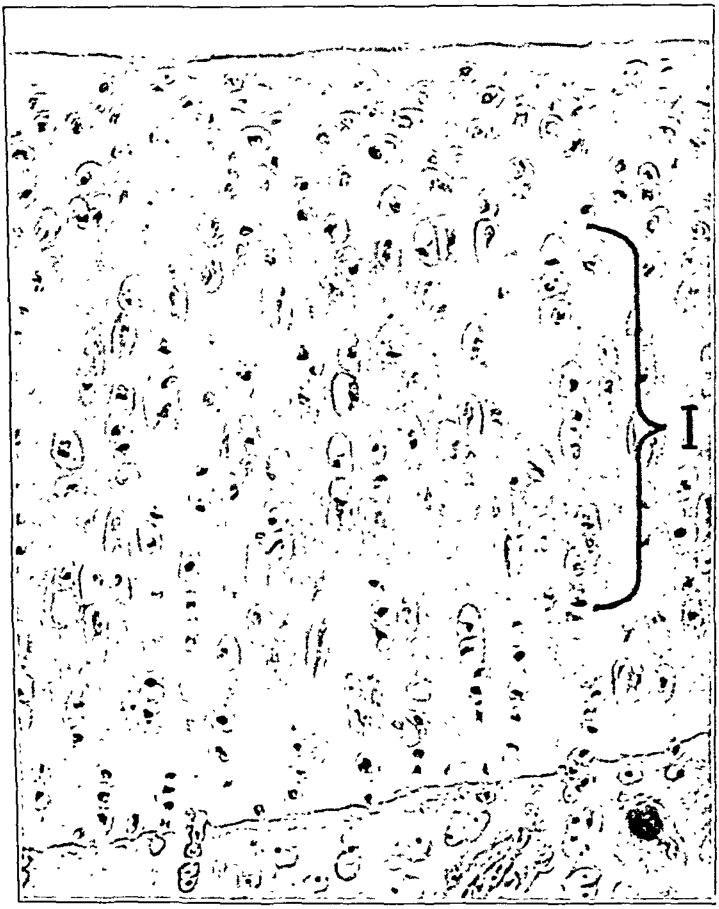

Fig. 3.—Photomicrograph (× 234) of the hyaline cartilage on the side of the joint (side of compression) opposite to the sprained ligaments, ten weeks after severe sprain. Note that many of the cartilage cells of the intermediate area (*I*) show only faint staining, while others have degenerated completely.

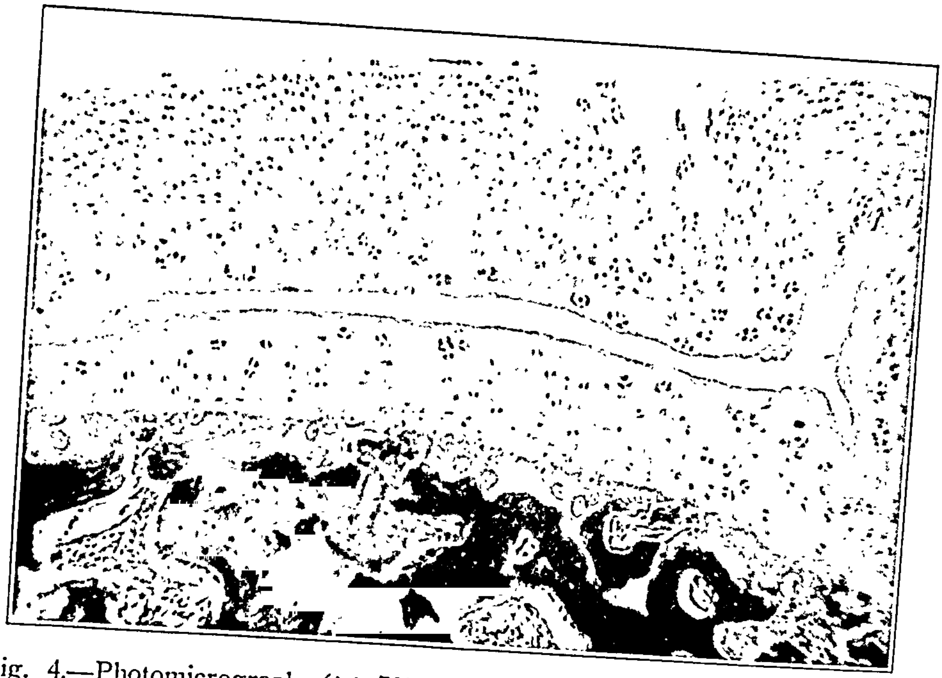

Fig. 4.—Photomicrograph (× 70) of the hyaline cartilage ten weeks after severe sprain. Note the horizontal fissure caused by trauma. Numerous necrotic cartilage cells may be seen at the margins of the fissure.

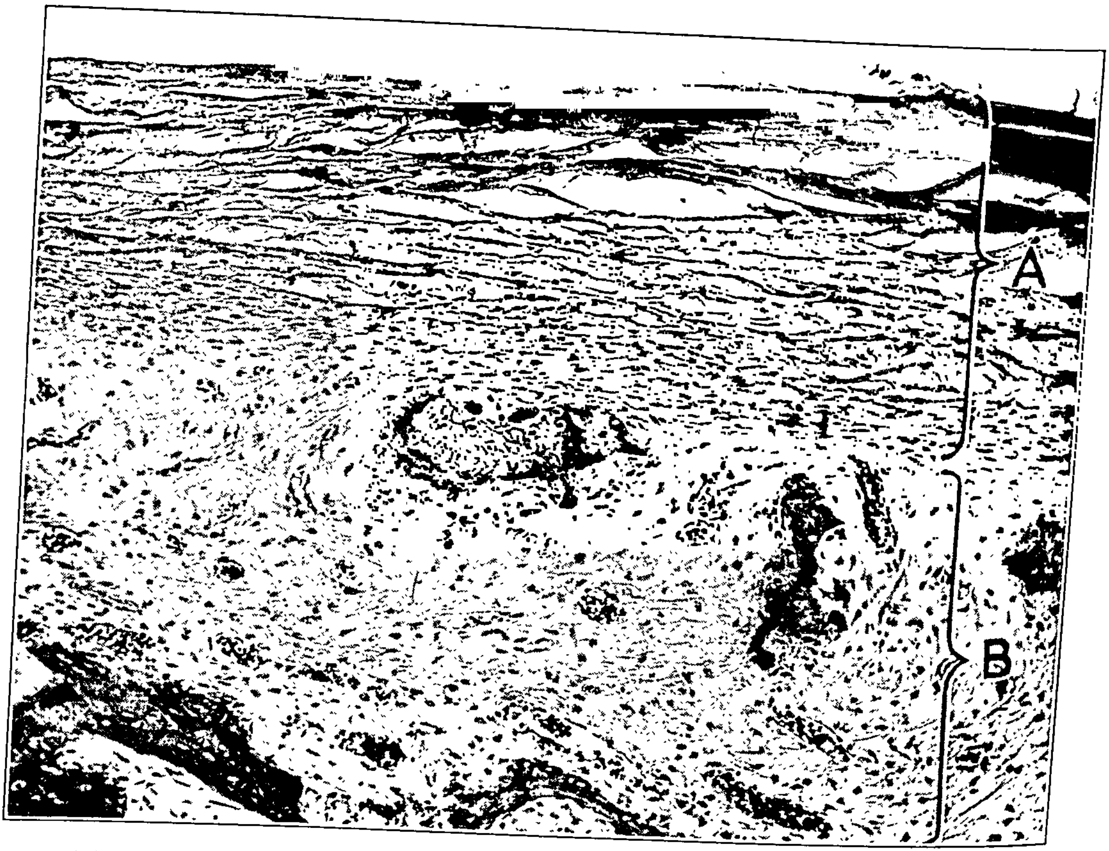

Fig. 5.—Photomicrograph (× 113) of the point of insertion of ligament into bone eight weeks after severe sprain. Note (*A*) the ligament and (*B*) the typical area of vascular callus with detached bits of bone which failed to cast a shadow in roentgenograms.

sprained ligaments showed numerous scattered cartilage cells, which were faintly or heavily eosinophilic in contrast to the normal cartilage cells which had taken up a deep basic stain. These eosinophilic cartilage cells showed other definite evidence of degeneration, such as fragmentation of the nuclei and shrinking of the cytoplasm (fig. 3). A horizontal fissure within the substance of the articular cartilage was found in one knee joint (fig. 4). In most of these specimens microscopic examination showed definite evidence of a tearing injury at the point of insertion of ligaments into the bone. Small bits of bone had been torn loose and tended to grow in the new location (fig. 5). At these points of insertion of ligaments there was a large increase of the fibroblasts with vascular dilatation and infiltration with round cells. Here, the process of repair persisted for as long as from eight to ten weeks. The synovial membrane showed a persistence of the previously described inflammatory changes for as long as from six to eight weeks.

COMMENT

These experiments demonstrate that trauma applied to joints causes an acute inflammatory reaction at the points of greatest injury. If the injury is severe enough, the bony or cartilaginous structures may be involved. These structures heal slowly under ordinary circumstances; therefore, the inflammation may become chronic. In the mild form of sprain there is an immediate response of the most vascular structures. The early increase in the activity of the synovial membrane with the exudation of synovial fluid is a condition which is known clinically as traumatic synovitis. At the same time there is edema of the loose subsynovial tissues and of the loose periarticular connective tissues, especially those near the tendon sheaths on the affected side of the joint. In the joints of the rabbits in group 1 (those with mild sprain) the external signs and gross evidence of pathologic change disappeared by the fourth week, but the microscopic evidence of inflammation (slight edema and fibrosis of the connective tissues) persisted until the end of the sixth week. This change is of clinical interest, since it suggests that the joint should be protected or supported for at least two weeks after the clinical signs have disappeared.

In the joints of the rabbits in group 2 (those with severe sprain without roentgenographic evidence of fracture) the inflammatory reaction of the soft tissues was similar in nature but more severe in degree than that found in the joints of the rabbits in group 1. The microscopic changes of the soft tissues usually persisted until the sixth to the eighth week and resolved gradually during the eighth to the tenth week. In addition to the microscopic changes found in the joints of the rabbits in group 1, there were evidences of injury at the point of insertion of ligaments into the bone and of the joint cartilage. At the ligamentous-osseous junctions detached bits of bone were usually seen. These bits of bone were microscopic in size and failed to throw a shadow in the roentgenograms.

Of greater interest were the changes in the intra-articular hyaline cartilage of the tibia on the side of the joint opposite to the sprained ligaments. Since the normal cartilage covering the surface of the tibia is approximately twice as thick as that which covers the convex surface of the corresponding condyle of the femur, it is believed that its intermediate or less compact area is more subject to a compression type of injury. The uniform finding of degeneration of the cells in the intermediate zone of the cartilage bears out this contention. It is further believed that this slow degeneration of the cartilage may produce not only local but remote effects on the more vascular structures of the joint and that therein lies one of the causes for the condition termed chronic traumatic arthritis. The traumatic fissure in this intermediate zone of the cartilage, although found in only one case, also adds evidence to show that this tissue is vulnerable to ordinary trauma.

SUBPHRENIC ABSCESS

AN ORIGINAL EXTRAPLEURAL OPERATION

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A subphrenic abscess may be defined as one which at some point is in contact with the under-surface of the diaphragm. Barlow described the condition in 1845, while Volkmann recorded the first operation in 1879.

It is my purpose to emphasize the importance of early diagnosis and operation, to report my cases and also an original, safer, transcostal, extrapleural method of drainage and to point out the necessity for choosing the most suitable operative route, depending on the location and the size of the abscess.

The subphrenic area is considered to be that space bounded above by the diaphragm and below by the transverse mesocolon. This space may be divided for clinical purposes into a suprahepatic and an infrahepatic space, and these may be divided into lesser but less completely separated spaces. A subphrenic abscess may occupy all or only a part of one or more adjoining spaces, depending on limiting adhesions.

The subphrenic space is divided as follows:

1. The suprahepatic space
    - Right intraperitoneal anterior superior space
    - Right intraperitoneal posterior superior space
    - Right extraperitoneal superior space, between the layers of the coronary ligament
    - Left intraperitoneal anterior superior space
2. The infrahepatic space
    - Right intraperitoneal inferior space
    - Left intraperitoneal inferior anterior space
    - Left intraperitoneal inferior posterior space (bursa omentalis)
    - Left extraperitoneal inferior retrosplenic space (Barnard[1])

A subphrenic abscess originates from a perforated peptic ulcer in about one third of the cases and from a suppurative appendicitis in

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Read before the Western Surgical Association, Dec. 12, 1935.

[1] Barnard, H. L.: Surgical Aspects of Subphrenic Abscess, Brit. M. J. **1**:371, 1908.

a third. It occurs frequently by direct extension from the appendix along the outer gutter of the ascending colon into Morison's pouch. Occasionally it may follow an infection or an injury to the liver, gallbladder, pancreas, colon, spleen or kidney or to other abdominal structures (Harper and Thomas[2]).

Rarely it may result from a metastatic infection, from extension of an infection from above the diaphragm or from osteomyelitis of a vertebra (Barnard).

The importance of the lymphatics in carrying infection from the colon and especially from the ileocecal region has been emphasized by Truesdale.[3]

Some abscesses which occur in the right posterior extraperitoneal space after a subsiding appendicitis, as in case 6, undoubtedly arise from infection along the lymphatics.

Subphrenic abscess occurs about three times more frequently in males than in females (Ochsner and Graves[4]). This may be due to the greater frequency of perforated peptic ulcer and of appendicitis in the male. Ochsner and Graves found that 70 per cent of the abscesses they observed occurred in persons from 9 to 40 years of age. They observed that only about 30 per cent of subphrenic infections went on to suppuration, the remainder subsiding spontaneously.

Anatomically, the superior surface of the liver, like the right surface and the most of the anterior surface, lies directly against the diaphragm and is curved corresponding to the dome of that structure. The superior surface reaches higher up on the right than on the left, while the center is slightly depressed. The junction of the superior and the posterior surfaces forms a rather blunt margin. The uneven posterior surface is shaped somewhat like a rectangular triangle. It is curved so as to be convex on the right side. From right to left may be found the fossa venae cavae, the impression for the adrenal gland, the lobus caudatus, the fossa ductus venosi and the impression for the abdominal esophagus. The liver is covered for the most part by the tunica serosa. There are four or five small areas and one fairly large one on the posterior surface of the right lobe which lie extraperitoneally.

Anteriorly, the ligamentum falciforme hepatis passes from the abdominal wall and the diaphragm near the midline to the superior surface of the liver. At the cardiac impression of the liver the two layers forming the peritoneal fold diverge from one another and go over into the anterior lateral layers of the ligamentum coronarium hepatis from the inferior surface of the diaphragm approximately in a frontal plane to the upper surface of the liver. The peritoneum forming the posterior layers of the coronary ligament comes from the posterior surface of the diaphragm or from the anterior surface of the right kidney, the adrenal gland or the flexura coli dextra and is sometimes called the ligamentum hepatorenale (Spalteholz[5] and Cunningham[6]).

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[2] Harper, F. R., and Thomas, C. A.: Subphrenic Abscess Following Trauma, J. A. M. A. **105**:1267 (Oct. 19) 1935.

[3] Truesdale, P. E.: Origin and Course of Infection in Subphrenic Abscess, Ann. Surg. **98**:846 (Nov.) 1933.

[4] Ochsner, A., and Graves, A. M.: Subphrenic Abscess: Analysis of 3,372 Collected and Personal Cases, Ann. Surg. **98**:961 (Dec.) 1933.

On the left the anterior and posterior layers of this ligament come together quickly and form the ligamentum triangulare sinistrum hepatis. At the right of the fossa venae cavae the anterior and posterior layers of peritoneum are widely separated, leaving a large uncovered area on the posterior surface of the liver, which is limited at the right by their junction into the ligamentum triangulare dextrum hepatis.

There is considerable normal variation in the level of reflection of the pleura at the costophrenic angles, forming a variable width of extrapleural diaphragm through which transcostal drainage of a subphrenic abscess might be established. Corning[7] pointed out that the height of the diaphragm varies at different ages. In the new-born infant it may be found at the level of the fourth rib on the right side. In a 36 year old man the diaphragm may be midway between the fifth and the sixth rib, while in a 72 year old man it may be below the sixth rib (fig. 1). In the presence of emphysema one will find the diaphragm lower than usual, and when there are old pleural adhesions it may be somewhat fixed, increasing the difficulties of diagnosis.

SYMPTOMS AND DIAGNOSIS

The symptoms of a subphrenic abscess vary to a large extent, depending on the source, location and size of the abscess. Elsberg[8] pointed out that they may develop days, weeks or months after an attack of appendicitis or an operation. Usually there is a history of a recent acute attack of appendicitis, cholecystitis, a perforated peptic ulcer or an operation. The temperature may persist or drop temporarily and then increase steplike each day, with an increase of systemic toxemia together with local symptoms of suppuration.

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[5] Spalteholz, W.: Atlas of Human Anatomy, ed. 3, translated by L. F. Barker, Philadelphia, J. B. Lippincott Company, 1910.

[6] Cunningham, J. D.: Text-Book of Anatomy, ed. 6, New York, William Wood & Company, 1931.

[7] Corning, H. K.: Lehrbuch der topographischen Anatomie für Studierende und Aerzte, ed. 3, Wiesbaden, J. F. Bergmann, 1911, p. 283.

[8] Elsberg, C. A.: A Contribution to the Pathology, Diagnosis, and Treatment of Subphrenic Abscesses After Appendicitis, Ann. Surg. **34**:729, 1901.

The peritoneum over the diaphragm is supplied from the phrenic nerve; consequently inflammation may cause referred pain in the shoulder and neck, where it is supplied by cutaneous nerves from the fourth

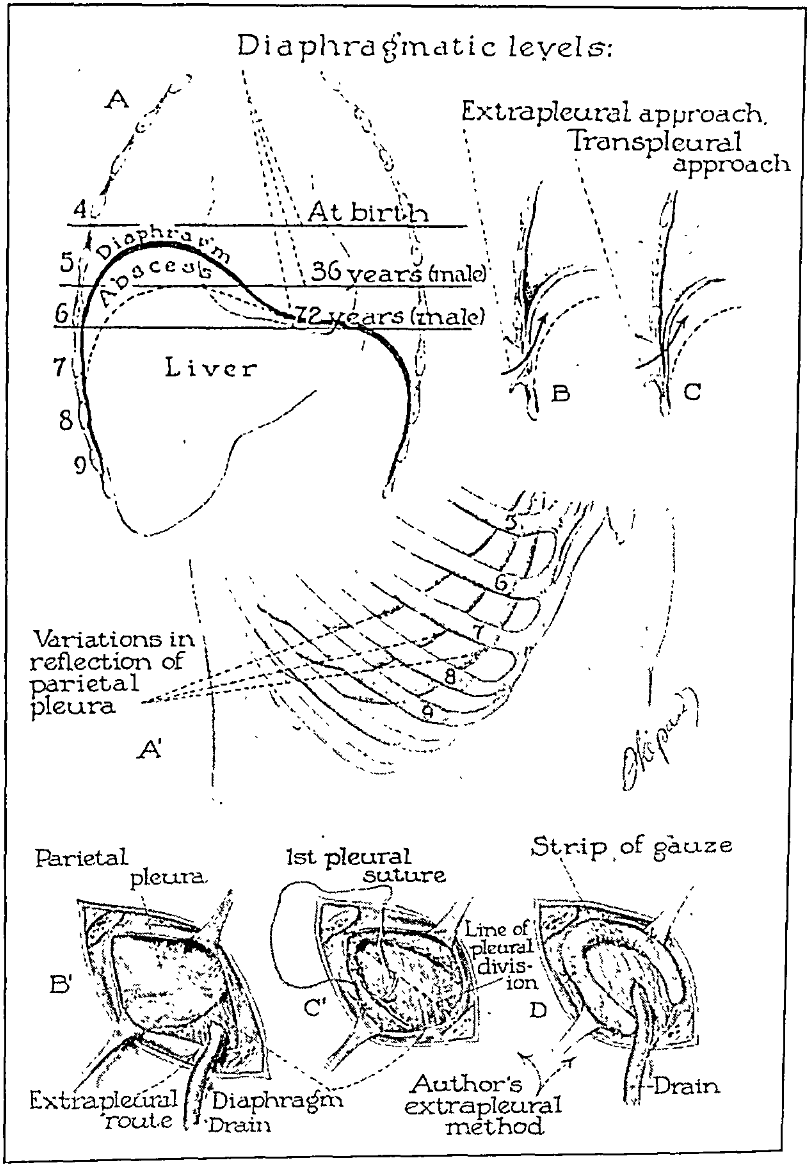

Fig. 1.—*A* and *A'* show normal variations in the height of the diaphragm and its pleural reflections. In *B* and *B'* is shown the transcostal extrapleural method of drainage, which may be used with a high pleural reflection; in *C*, the transcostal route which is frequently used to open the pleural cavity in the absence of adhesions; in *C'* and *D*, my method. In the last method, after resection of one rib in the axillary line, the costal and diaphragmatic pleural layers are incised, and the edges are dissected laterally and sutured, forming an extrapleural area on the diaphragm for drainage.

cervical segment (Christopher [9]). The lateral and anterior portions of the abdominal peritoneum are supplied by the lower intercostal and first lumbar nerves, and the central posterior and the pelvic portions of the peritoneum, chiefly by the sympathetic system (Cope [10]).

At the onset there may be limited or painful respirations owing to immobilization of the diaphragm or to a pleuritis, which is more marked in the case of a suprahepatic abscess and less noticeable when the abscess is located below the reflection of the pleura. Later there is practically always limitation of movement of the diaphragm, but the amount of elevation is variable, depending on the size and location of the abscess.

A fluoroscopic examination or roentgenograms taken from several angles and with the patient upright may fail to demonstrate a small suprahepatic abscess. When the abscess is large there may be extension forward and downward, with a visible swelling and an area of dulness over the abdomen forming a triangle bounded by the falciform ligament, the transverse colon and the right costal border.

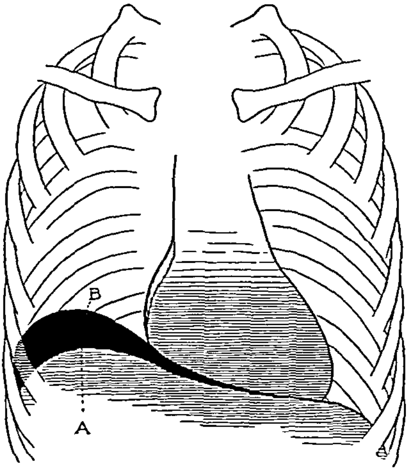

Fig. 2 (case 3).—Drawing made from roentgenograms which at the onset of symptoms showed only slight elevation of the diaphragm (*A*), but one week later (*B*) there wete marked elevation of the diaphragm and also distortion of the heart due to an abscess of the superior anterior space which contained no gas.

In cases in which the diagnosis is doubtful examinations should be repeated in a few days, and a comparison made of the level and immobility of the diaphragm (fig. 2 *A*-*B*). In a few cases gas and a shifting fluid level can be demonstrated both by roentgenographic and by physical examination (fig. 3).

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[9] Christopher, Frederick: Neck Pain in Subphrenic Abscess, Ann. Surg **85**:318, 1927.

[10] Cope, V. Zachary, in Walton, A. J.: A Text-Book of Surgical Diagnosis, New York, William Wood & Company, 1928, chap. 2, p. 697.

The early friction sounds and symptoms of pleuritis over the costophrenic region may disappear with effusion in the pleural cavity. It is often difficult to establish a differential diagnosis between abscess and bronchitis, pulmonary inflammation, pleuritis or atelectasis. The diagnosis was correct in only 38 per cent of the 18 cases reported by Brown.[11] Fever and the degree of toxemia, as indicated by a marked leukocytosis, vary with the acuteness and activity of the abscess but are increased out of proportion to the pulmonary findings.

An abscess involving the suprahepatic posterior intraperitoneal space may differ roentgenographically from one involving the anterior space in that in the anteroposterior view of the former the costophrenic instead of the cardiophrenic angle is obliterated and in the lateral view the posterior instead of the anterior costophrenic angle is obliterated.

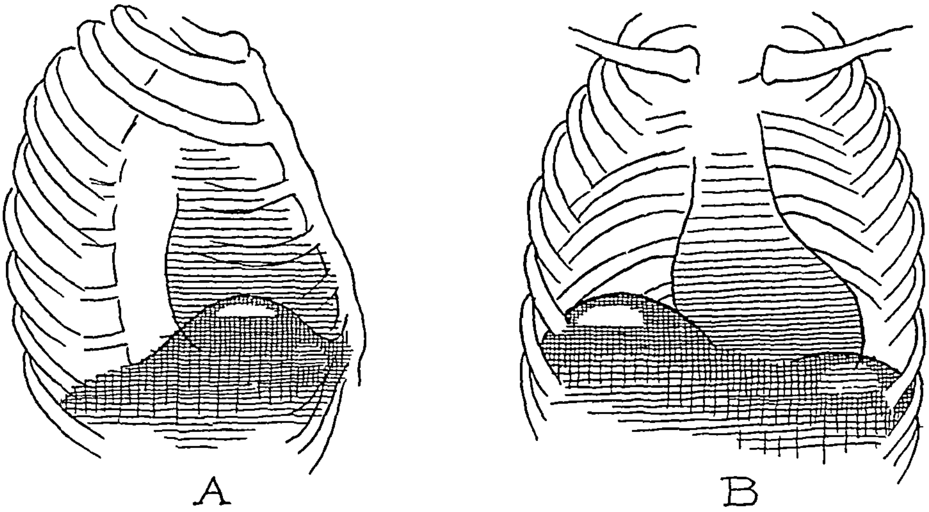

Fig. 3 (case 4).—Elevation of the diaphragm due to an abscess containing gas. There was slight increased density in the lower lobe of the lung. Transcostal extrapleural drainage was done (fig. 1, *C′* and *D*).

When the abscess involves the right posterior extraperitoneal space the roentgenograms may show little elevation of the diaphragm, although in the lateral view the posterior costophrenic sinus may be obliterated.

In the case of a large subphrenic abscess the roentgenograms may show a patchy area of increased dulness in the lower lobe of the lung, which may be definitely above the lower edge, the result of atelectasis or peribronchial inflammation following immobilization and elevation of the diaphragm. There are frequently increased hilus markings in both lungs, especially in the right.

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[11] Brown, H. P., Jr.: Subphrenic Abscess, Ann. Surg. **93**:1075, 1931.

In the case of a subhepatic abscess on the right side the liver may push the diaphragm up with limitation of motion, but there is no gas beneath it.

If the abscess is large there may be an abdominal swelling beneath the liver or in the loin in addition to local tenderness, muscle spasm and rigidity.

Dulness from a subhepatic abscess may extend below the liver, outlining the triangle formed by the falciform ligament, the transverse colon and the costal border, similar to that caused by an abscess of the anterior suprahepatic space. Tenderness and bulging in the right loin occur frequently with a subhepatic abscess as well as with an abscess in the posterior superior space.

Diagnosis is often delayed, even when there are positive roentgenographic signs, owing to the lack of clinical recognition of the condition. When there is gas beneath the diaphragm, physical examination with the patient in the recumbent position may show diminution or absence of hepatic dulness anteriorly and a high axillary dulness which shifts when the patient turns or sits up.

A persisting local tenderness is quite suggestive. A widening of the right side of the chest due to elevation of the lower ribs was observed in case 5, that of an extraperitoneal abscess, without elevation of the diaphragm.

The first symptoms may be either thoracic or abdominal and vary from pleuritis, jaundice, a local swelling and pain or tenderness to those of a spontaneous perforation.

There is often an incubation or quiescent period of a week or ten days, the only symptoms being slight fever and an increased leukocytosis.

After an abscess has formed a defense zone of adhesions, the earlier it is drained the less will be the chances of a fatal issue as a rule. One might suggest delay to permit development of further overlying pleural or peritoneal adhesions, except that rupture, sepsis and pyemia may suddenly develop. Usually after a brief period the abscess increases rapidly in size, and the toxic symptoms become marked. There may be extension of infection through the diaphragm into the pleural cavity, retroperitoneally by way of the lymphatics into the mediastinum or into the peritoneal cavity.

The less frequent intrahepatic abscess is more likely to produce chills and pain referred to the region of the right scapula (Elsberg). A foul odor is more likely to be associated with a subphrenic than with a hepatic abscess. A perinephritic abscess should give rise to some evidence of renal infection, and the intravenous urogram will aid in the diagnosis.

One should consider the possibility of a postoperative subphrenic accumulation of bile due to leakage or injury of the bile ducts, as in the following case.

Recently I removed 3,000 cc. of sterile bile from the right superior anterior subphrenic space, which extended down to the transverse colon. The patient, a 32 year old man, had been operated on three weeks before by another physician, who removed the gallbladder and gallstones. The drain was removed on the second day, and the wound healed. At the operation a segment of the hepatic duct had been excised, and sterile bile had collected beneath the diaphragm with limiting adhesions of the colon. There was little jaundice for the first ten days and slight elevation of the diaphragm. The patient was very weak after the operation and became progressively worse, with little fever and acholic stools. Shortly before drainage, the jaundice became intense, and there was marked elevation of the diaphragm.

After the wound was reopened and the bile drained, I found that the cut ends of the hepatic and common ducts were too indurated and widely separated to suture. A gap of 1 inch (2.5 cm.) was bridged with a rubber tube which extended into the duodenum. Drainage of bile stopped after six weeks.

The patient has gained 30 pounds (13.6 Kg.) and is well after three months.

PROGNOSIS

The prognosis of a subphrenic abscess is always grave, and it is important to operate before the development of sepsis or intrathoracic complications.

The mortality from subphrenic abscesses is somewhat variable but always high (Giertz[12]). Lockwood[13] reported it to be 33.3 per cent in the cases in which operation was performed and 96.8 per cent in those in which it was not performed. Ochsner and Graves found it to be 32 per cent in their cases of abscess, in which the sources varied, while Bevan[14] stated that it was about 50 per cent in cases of abscess which occurred following appendicitis. Some complications are unavoidable, owing to extensive peritonitis or to a severe original infection.

Aspiration of a subphrenic abscess should be avoided before and if possible at operation, since it is likely to result in empyema or peritonitis, unless adhesions which are difficult to demonstrate are present.

Lockwood found that 41.9 per cent of deaths were due to intrathoracic complications.

Ochsner and Graves found that of 189 patients who were operated on without the pleura or the peritoneum being opened, 21 per cent died; of 305 on whom transpleural drainage was done, 39 per cent died, and of 307 on whom transperitoneal drainage was done, 35.5 per cent died. In 7 cases of their own in which the pleural cavity was opened at operation, the mortality was 85 per cent.

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[12] Giertz, K. H.: Twenty-Five Years' Experience in the Treatment of Peritonitis, Ann. Surg. **104**:712, 1936.

[13] Lockwood, A.: Subdiaphragmatic Abscess, Surg., Gynec. & Obst. **33**:502, 1921.

[14] Bevan, A. D.: Present Status of the Problem of Appendicitis, S. Clin. North America **16**:63, 1936.

Barnard reported the development of empyema in 56 of 76 reviewed cases.

A patient with chronic empyema which developed after a drainage operation for subphrenic abscess came under my care recently.

Three months previously this 26 year old man was operated on, and a ruptured appendix was removed four days after the onset of symptoms, with drainage. Ten days later pain developed in the right upper abdominal quadrant, and after five days' observation, including roentgen examination, a subphrenic abscess was drained. The ninth and tenth ribs were resected posteriorly, followed by drainage and healing of the wound. Immediately after the operation the patient suffered from severe pain in the right side of the chest with dyspnea. The pain gradually became worse, and one month later 4 quarts (3.7 liters) of pus was drained from an empyema on the right side. The drainage tube was removed too soon, and the patient came into the hospital quite toxic.

Immediately after the insertion of a catheter into the old sinus and drainage of a large empyema cavity, he obtained relief, but further surgical treatment will be necessary.

There is a need for a safer one stage transcostal drainage operation in which the pleural cavity need not be contaminated. The anterior and posterior subcostal incisions are too far from the small suprahepatic abscesses, which makes it difficult to avoid opening and contaminating the peritoneal cavity.

AUTHOR'S CASES

In my 9 cases all the patients were males. Two deaths occurred, making a mortality of 22.23 per cent. In all the cases the abscess was on the right side, and a drainage operation was performed in each. The ages of the patients varied from 14 to 59, the average being 34. The ages of the 4 patients having perforated ulcers varied from 32 to 59. the average being 42, while the ages of the 4 with appendicitis varied from 14 to 52, the average being 25.

There were 2 cases of perforated duodenal ulcer and 2 of perforated gastric ulcer, in 3 of which operation was performed.

There were 4 cases of acute appendicitis, in only 1 of which had operation been performed, and then for a pelvic abscess.

The length of time from rupture of the viscus or the onset of acute appendicitis to the onset of symptoms of the subphrenic abscess varied from one to sixteen days and it averaged eight days. The symptoms were then present from eight to thirty-nine days and averaged nineteen days before drainage. This was an average of twenty-seven days from the onset of the original infection to operation.

The temperature during most of the course of the abscess was rarely over 102 F., but before operation there was usually a steplike rise, with increased toxemia and a slight drop in the white cell count. The number of white cells varied from 7,000, a count made after per-

Data on the Author's Nine Cases of Subphrenic Abscess

Case	Sex	Age, Years	Source of Abscess and Days Before Drainage	Previous Operation	Time Between Onset of Source to Onset of Symptoms, Days	White Blood Cell Count	Location of Abscess in Subphrenic Space; Contents of Abscess	Method of Drainage	Complications and Result
1	M	59	Perforated duodenal ulcer; 39	0	0	21,900	Right superior anterior space; 2,000 cc. + gas	Transcostal route, 10th rib; extrapleural method	Cured; sinus 5 mo.
2	M	46	Perforated gastric ulcer; 22	+	11	30,900	Right superior anterior space; 2,000 cc.	Transcostal route, 10th rib; extrapleural method	Died; moribund at operation; bilateral bronchopneumonia
3	M	32	Perforated gastric ulcer; 46	+	18	10,240	Right superior anterior space; 300 cc.	Transcostal route, 9th rib; extrapleural method	Cured 1 yr. and 9 mo.; sinus 2 mo.
4	M	32	Perforated duodenal ulcer; 15	+	6	28,150	Right superior anterior space; 500 cc. + gas	Transcostal route, 8th rib; author's extrapleural method	Cured 1 yr.; sinus about cartilage; resected 4 mo. later
5	M	17	Acute appendicitis; 35	0	7	20,950	Right extraperitoneal superior space; 500 cc. Staph. albus on culture	Posterior transcostal route, 12th rib	Cured; sinus 2 mo.
6	M	14	Appendicitis with perforation; 17	0	9	16,300	Right superior posterior space; 1,000 cc.	1. Transcostal route, 10th rib; exploration of peritoneal cavity extrapleurally 2. Posterior subcostal route, 12th rib	Cured; pelvic abscess drained by rectum before symptoms of subphrenic abscess developed
7	M	18	Appendicitis with perforation; 15	0	6	20,900	Right superior posterior space; 800 cc.	Posterior subcostal route, 12th rib	Died 10 days postoperatively; bronchopneumonia of left lung and empyema
8	M	52	Appendicitis with perforation; 23	0	9	14,400	Right superior posterior and right inferior spaces; 3,000 cc.	Posterior subcostal route, 12th rib	Cured; sinus 2 mo.
9	M	42	Perforated gallbladder; 35	0	10	7,000	Right inferior and part of right superior anterior spaces; 75 cc.; colon bacilli on culture	Anterior subcostal route; right rectus incision; cholecystectomy and drainage	Cured 3 yr.; sinus 3 wk.

foration of a gallbladder, to 30,900, a count made twenty-two days after an operation for a perforated gastric ulcer, which was associated with bilateral pneumonia and terminated fatally. The average count made just before drainage was 18,900. With one exception, there was a higher white cell count in the cases in which the abscess was large. In this case the white cell count was 14,400 and there was 3,000 cc. of pus in the abscess cavity twenty-three days after the onset of appendicitis which was not treated surgically.

The symptoms suggesting a subphrenic abscess were first noted in the side of the chest in 4 cases, in 3 after a perforated ulcer and in 1 after appendicitis, while in 5 cases the first symptoms were abdominal, in 1 after an ulcer, in 3 after appendicitis and in 1 after perforation of the gallbladder.

The correct diagnosis was made before operation in 8 cases, or 88 per cent.

The subphrenic abscess was in the right anterior superior space in 4 cases, in all of which it followed a perforated ulcer. In 4 cases the abscess followed acute appendicitis; it was located in the right extrapleural superior space in 1 and involved the right posterior superior space in the other 3. In one of the latter it extended forward to the anterior abdominal wall into the inferior space and contained 3,000 cc. of pus.

In the case in which there were two separate perforations of the gallbladder there were two abscess cavities, one inferior to the liver and a smaller one just above the edge of the liver.

The size of the abscess varied from 75 to 3,000 cc., the average size being 1,040 cc. There was little difference in the size of the abscesses which developed following a perforated ulcer and of those which occurred after acute appendicitis.

There was gas in two abscess cavities, or 22 per cent, both of which occurred after perforated ulcers. The pus had a foul odor in 3 cases. Staphylococcus albus was cultured from the pus of an abscess which occurred after appendicitis, and colon bacillus was cultured from the pus of the one which occurred after a perforated gallbladder.

In 1 case in which abscess followed a perforated ulcer there was extensive bronchopneumonia on each side, and the patient was moribund at operation.

The other death was due to involvement of the opposite lung with pneumonia and empyema ten days after operation.

Most of the operative wounds drained from one to three months, but in 2 instances the period of drainage was longer and there were no recurrences.

The persistence of the high diaphragm laterally after a month of drainage, as shown by roentgenograms in cases 6 and 8, was probably due to extensive adhesions, which explains the slow obliteration of these abscess cavities.

There have been no complaints as a result of the abscess and operation.

There was a recurrence of symptoms of ulcer in 1 case a year later, which necessitated medical treatment.

OPERATIVE TREATMENT

Drainage of a subphrenic abscess may be obtained through one of four regions, depending on the location and size of the abscess. The transcostal route may be chosen either anteriorly in the axillary line or posteriorly through the twelfth rib. The subcostal route may be used anteriorly through the abdomen or posteriorly beneath the twelfth rib and the level of the pleural reflection.

If the abscess is localized above the liver in the anterior superior space and beneath the dome of the diaphragm, extrapleural drainage should be established by resection of a rib in the axillary line directly above or as close to it as possible.

If an abscess is small, one may choose to resect the eighth rib, while for the larger abscesses, which extend lower, the ninth or tenth rib should be resected, since there is a wider extrapleural part of the diaphragm in this region and drainage should be established both as low and as posteriorly as feasible.

Elsberg has described the trancostal operation with resection of two ribs, the ninth and the tenth.

He established drainage through the diaphragm below the pleural reflection when it was possible, while in other cases he first obliterated the pleural cavity around the operative area by a circular suture between the pleural layers.

Occasionally the pleural cavity may be obliterated in this region by adhesions, or the pleural reflection may be elevated by pressure from the abscess (Boeckel[15]).

Lilienthal[16] and Parijsky[17] have been able to mobilize the costophrenic reflection of the pleura and push it upward, but Brown stated that this was not practical owing to frequent adhesions. It also necessitates the resection of two or more ribs, and the pleura may be torn and the pleural cavity contaminated.

While most surgeons attempt to obliterate the pleural cavity either by a circular suture or by a gauze pack, these procedures are not always satisfactory, even if the abscess is drained a few days later, as shown by frequent secondary empyema and high mortality (Elsberg and Ochsner and Graves).

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[15] Boeckel, cited by Ochsner and Graves.[4]

[16] Lilienthal, H., in discussion on Ochsner and Graves,[4] p. 990.

[17] Parijsky, cited by Ochsner and Graves.[4]

Immediate drainage is usually advisable, since a few days' delay may result in sepsis and pulmonary complications.

In 4 of my cases the abscess was in the right anterior superior space and either localized beneath the dome of the diaphragm or extended well forward and laterally.

In cases 1, 2 and 3 I resected either the ninth or the tenth rib in the axillary line and opened the abscess through the diaphragm, below the pleural reflection, without opening the pleural or the peritoneal cavity (fig. 1 *B* and *B'* and fig. 2).

Since there is no test for determining the level of the costophrenic reflection, one cannot always avoid opening the pleural cavity in a transcostal operation unless adhesions are present or the pleural reflection is high.

In case 4 there was a relatively small localized abscess under the dome of the diaphragm (fig. 3). The eighth rib was resected in the anterior axillary line, and the pleural cavity, which extended quite low, was opened (fig. 1 *C*). A delay of several days before drainage of the abscess would have been necessary if the usual obliterative methods of suture or packing of the pleural cavity had been used, and there would have been the additional danger of empyema.

An original and simple method was devised to obliterate the pleural cavity and at the same time to make an extrapleural area of the diaphragm which could be safely incised, with immediate drainage of the abscess (fig. 1 *C'* and *D*).

The patient (case 4), a man aged 32, entered the hospital on June 13, 1935, complaining of severe pain in the upper part of the abdomen for three hours associated with vomiting. There were no previous symptoms, except that during the last two weeks he had noticed some gastric distress from one to two hours after meals, which was relieved by rest.

The past history was unimportant, except for an operation for removal of the appendix several years previously.

Physical examination revealed marked rigidity over the entire abdomen and a decreased area of hepatic dulness. The white cell count was 9,300.

An emergency operation was performed six hours after the onset of symptoms, and a perforated ulcer of the duodenum was sutured, with aspiration of free fluid.

Convalescence was good until the tenth day, when the patient had a temperature of 101 F. On the eleventh day there was some pain on the side of his chest and a leukocyte count of 28,150. On physical examination there were diminished breath sounds posteriorly and a lack of respiratory excursion of the diaphragm but no râles. With the patient in the recumbent position an area of high axillary dulness and one of tympany were noted over the region of the liver anteriorly. When he turned to either side the area of dulness and that of tympany shifted, suggesting a subphrenic abscess containing gas.

Fluoroscopic examination and roentgenograms showed an abscess cavity containing gas under the right side of a high fixed diaphragm (fig. 3).

Operation was performed on June 28, 1935, my original technic of transcostal extrapleural drainage being employed.

A local anesthesia was used, and about 2 inches (5 cm.) of the eighth rib was resected as low as possible in the anterior axillary line. The pleural reflection was so low that it was impossible to push it up without resecting another rib and perhaps accidentally opening the pleural cavity. A longitudinal incision was made through the costal pleura in the bed of the resected rib, starting about 1 cm. from the upper end (fig. 1 *C′*). This pleural incision was continued downward to the pleural reflection and then upward through the diaphragmatic pleura to a point below the beginning of the anterior incision. The two edges of the diaphragmatic pleura with a thin layer of the underlying muscle were then dissected laterally. The lower edge of the pleura was widely approximated and sutured with two rows of fine catgut, without tension, to the overhanging free edge of the costal pleura and intercostal muscles, completely obliterating the pleural cavity. This suture line was completely covered with a narrow strip of gauze impregnated with petrolatum, which was sutured securely over it with fine catgut (fig. 1 *D*).

This procedure, with resection of only one rib, provided an extrapleural U-shaped diaphragmatic area about 3 cm. long and 1.5 cm. wide, which was entirely satisfactory for drainage of the underlying abscess. A small aspirating needle was inserted through this extrapleuralized portion of the diaphragm, and an abscess containing about 500 cc. of pus was located and opened by means of a small incision.

Convalescence was uneventful, with no symptoms of pleuritis, and the patient left the hospital one month later with a small amount of drainage. The cavity healed after about two months, but a sinus persisted at the lower end of the wound around the overlying cartilage. This was resected three months later, and the patient has had no further complaints.

On examination one year and nine months after operation the lungs showed no pleural thickening. The patient had regained his normal weight and had been working steadily for over one year.

For the suprahepatic abscess, one rubber tube is usually sufficient for drainage. For the large abscess associated with marked toxemia, a gradual decompression may be advisable.

The drainage tube should be sutured to the skin and daily irrigation employed. The size of the cavity should be determined from time to time by the injection of fluids or by roentgenographic visualization, and the tube should be shortened occasionally as obliteration occurs.

The abscesses of the subhepatic and posterior spaces may be drained more freely, but one should avoid extensive manipulation, and the forceful rib-spreading exploration of Lockwood in order to locate multiple cavities should be rarely necessary.

If a subphrenic abscess points in the upper part of the abdomen, extending forward either from the right superior anterior space or from the subhepatic space, it may be drained through an anterior abdominal incision.

The larger of these abscesses are limited medially by the falciform ligament, below by the transverse colon, which becomes adherent to the anterior wall, and laterally by the costal arch, which forms a bulging triangle of dulness in the upper portion of the abdomen.

The abdominal route was used in a majority of all cases reported by Gatewood.[18] However, there is danger of opening the general peritoneal cavity unless the abscess is walled off by adhesions well below the incision. Either a high rectus or an oblique subcostal incision may be used to drain an abscess pointing in this region.

The subcostal approach of Clairemont and Meyer[19] is intended to drain a high-lying suprahepatic abscess extraperitoneally. This incision extends parallel to the costal margin down to the peritoneum, which may be separated from the diaphragm by the finger without tearing it until the abscess is reached.

In case 9 of my series, after a perforation of the gallbladder from stones abscess cavities were localized beneath the liver and between it and the abdominal wall. The general peritoneal cavity was opened through a right rectus incision and both cavities opened and found to contain gallstones. The markedly diseased and perforated gallbladder, which contained other stones, was removed, with drainage anteriorly, and recovery resulted.

A large subhepatic abscess may point both posteriorly and anteriorly, but the posterior drainage route beneath the twelfth rib into Morison's pouch is usually easier and safer and provides better drainage than the anterior route.

If the abscess is localized in the upper part of the posterior superior space or above that in the extraperitoneal space, the twelfth rib may have to be dislocated upward, or resected as advocated by Ochsner and Graves, and the peritoneum separated from the under-surface of the diaphragm until the abscess is reached. In either instance, but especially in the latter, the costophrenic sinus may be found obliterated with the abscess directly against the lower ribs.

In cases 6, 9 and 8 the right posterior superior space was involved, with bulging in the loin. In case 6, in which the bulging extended well forward, the tenth rib was resected, the peritoneal cavity was explored through the extrapleural part of the diaphragm and the abscess was opened well back under the liver. A second small incision was made posteriorly beneath the twelfth rib directly into the abscess cavity, and drains were inserted. The peritoneal cavity around the transcostal extrapleural incision was walled off with an iodoform gauze pack, and the patient had an uneventful convalescence.

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[18] Gatewood: Subphrenic Abscess, Am. J. M. Sc. **180**:398, 1930.

[19] Clairemont, P., and Meyer, M.: Erfahrungen über die Behandlung der Appendicitis, Acta chir. Scandinav. **60**:55, 1926.

In case 7 the abscess bulged only in the loin, while in case 8 it pointed both in the loin and anteriorly, with a large triangle of dulness. In each case the abscess was drained posteriorly by an incision beneath the twelfth rib, but in spite of this in case 7, one of extensive primary peritonitis, a fatal suppuration developed in the opposite lung, associated with empyema.

Posterior drainage beneath the twelfth rib is accomplished by the following technic:

A transverse incision is made posteriorly at the level of the spinous process of the first lumbar vertebra, which will avoid the danger of opening the pleural cavity (Cunningham). The latissimus dorsi and the external oblique muscles and the deep fascia just lateral to the erector spinae muscles are split, and exploration for the abscess is made by blunt dissection beneath the peritoneum. Large abscesses extending downward and into the posterior superior pouch of Morison are easily palpated and opened into directly beneath the incision, and it is undesirable and rarely necessary to aspirate for diagnosis. Two large fenestrated rubber tubes, which are not too stiff or too long, are inserted for drainage and sutured to the skin with silkworm gut, and the wound with its separated muscle fibers is left open.

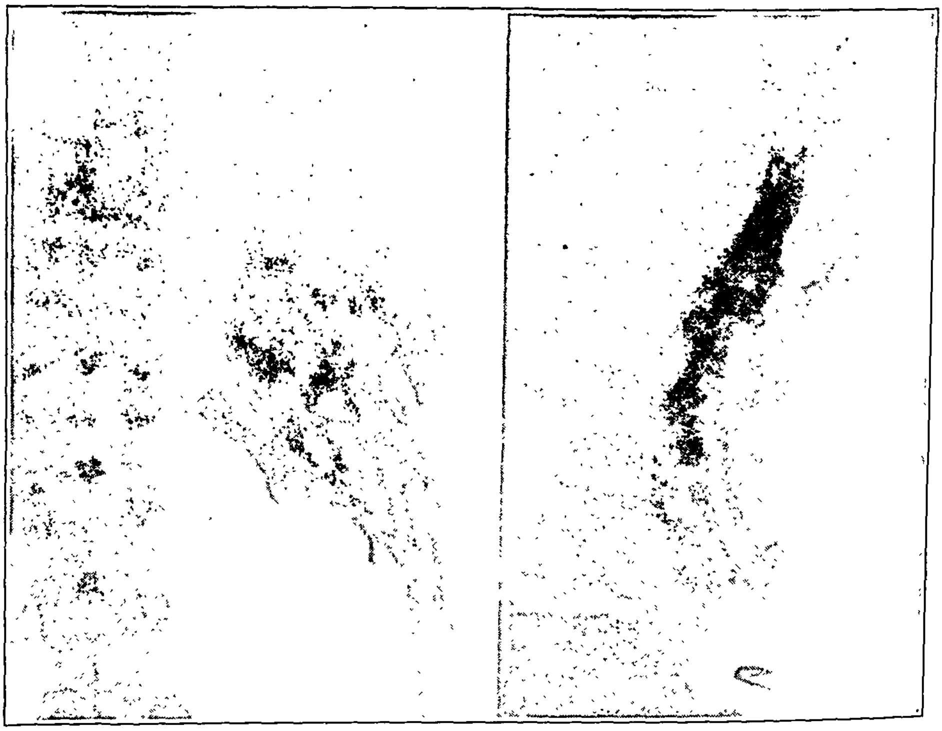

Fig. 4 (case 5).—Roentgenographic visualization of the right extraperitoneal abscess cavity ten days after resection of the twelfth rib and drainage. Elevation of the diaphragm was not present before operation.

High-lying abscesses behind the liver may be opened by blunt separation of the peritoneum upward; occasionally a rib resection may be necessary, unless Bevan's method of forcefully dislocating the twelfth rib upward provides enough exposure.

In case 5 the abscess was limited to the right extraperitoneal space posterior to the liver and above the level of the twelfth rib. The subcostal approach was made, and the inferior surface of the liver was palpated without opening the peritoneum or locating the high-lying abscess. The edges of the skin and muscles were then retracted higher up, and the twelfth rib was resected. The lower edge of the abscess, which contained 500 cc. of pus, was opened posterior to the liver in the bed of the resected twelfth rib and drained with two large rubber tubes (fig. 4).

In reviewing the operative procedures in my cases, 3 of the 4 abscesses of the superior anterior space were easily drained through the extrapleural portion of the diaphragm by the anterior transcostal operation. In the fourth case the pleural cavity was satisfactorily excluded, and extrapleural drainage was established by an original procedure.

Resection of the twelfth rib by the posterior route was necessary in case 5, in which the abscess was in the right extraperitoneal space.

In case 9 the peritoneal cavity was opened anteriorly.

In 3 cases an abscess of the posterior superior space pointed in the loin, and drainage was done posteriorly beneath the twelfth rib.

CONCLUSIONS

1. One should make every effort to diagnose a subphrenic abscess from the first symptoms, especially when the patient fails to improve satisfactorily after an attack of appendicitis, a perforated ulcer or any abdominal infection or operation.

The onset of symptoms is usually within a week or ten days after the original infection but may develop weeks or months later. Repeated comparative examinations may be necessary for diagnosis.

A quiescent period may precede the onset of symptoms, but no time should be lost before establishing drainage, because the sudden development of sepsis and pulmonary complications is the major factor in the high mortality.

2. Complications may be largely avoided by early drainage with the method most suitable to the location and size of the abscess.

3. An original transcostal operation is reported by means of which immediate extrapleural transcostal drainage may be established.

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INJECTION OF ETHER INTO THE BILIARY TRACT AS TREATMENT FOR CHOLEDOCHOLITHIASIS

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In recent years great strides have been made in the study of the chemistry and physiology of the biliary tract. This increase in knowledge, however, has not altered the position pathologic conditions of the biliary tract hold as formidable opponents of the surgeon's diagnostic and technical skill. In reviewing causes for some of the unsatisfactory surgical results, we find stones in the common duct to be one of the most frequent offenders. The simple case of a large stone high in the common duct, with a typical history of obstruction of the biliary tract, of course, offers no difficulty. However, the small stones low in the common duct frequently remain undiagnosed before and even during operation. Many observers have called attention to the symptomatic silence of this condition. Clute,[1] in reviewing seventy-nine cases of stones in the common duct, found that there was no history of jaundice in twenty-nine. Lahey[2] found that in 39 per cent of his cases of stones of either the common or the hepatic ducts there was absence of jaundice; he called particular attention to the frequency with which small stones low in the duct were overlooked at operation. From time to time many articles have appeared advocating different procedures or instruments for discovering and removing these stones. Nevertheless, in this regard the surgical world is still far from Utopia, and the present status was aptly described by Clute and Swinton[3] when they stated that "as yet we have no means at our command which will determine positively after exploration of the common duct that every stone has been removed." Besides failing to guarantee removal of the stones, exploration of the common duct definitely increases the mor-

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From the David May Surgical Research Fund of the Jewish Hospital, and the Surgical Department of Washington University School of Medicine.

[1] Clute, H. M.: Common Duct Stones Without Jaundice, S. Clin. North America **11**:261-269 (April) 1931.

[2] Lahey, F. H.: Incidence and Management of Stones in Common and Hepatic Ducts, Ann. Surg. **98**:644-649 (Oct.) 1933.

[3] Clute, H. M., and Swinton, N. W.: Exploration of Common Duct in Gall-Stone Surgery, Surg., Gynec. & Obst. **59**:906-912 (Dec.) 1934.

tality for operations on the biliary tract. Consequently, any method which would obviate this procedure and still lead to the removal of the stone could be counted as a distinct advance.

Since the discovery by Vollisnieri[4] in 1722 that gallstones were soluble in alcohol and turpentine, innumerable ideas have been presented for the use of lipoid solvents in the treatment of biliary stones. Many years ago (1908) Wright[5] reported a case in which stones were impacted into a mass in the common duct and could be removed only after the injection of 1 drachm (3.7 cc.) of turpentine directly on the impaction. In 1932 Pribram[6] reported a case of cholodocholithiasis, in which the stone was tightly lodged in the papilla of Vater, with successful treatment by the daily injection of ether into the common duct. Later (1935) he[7] reported five cases of "sepsis and cholemia" in which stones in the common duct were also successfully treated by his method, which consisted of the insertion of a tube into the common duct down to the obstruction and the daily injection of "several cubic centimeters of ether" on the stones. In addition to the ether, he mentioned irrigations with sodium chlorate. From time to time he checked the progress of the obstruction fluoroscopically after the injection of iodized oil into the common duct.

The purpose of our work was, first, to investigate the effects of ether, a lipoid solvent, as injected directly into the biliary tract with obstruction of the common duct and, second, to determine whether or not ether would dissolve the ordinary stones under conditions simulating incarceration in and blockage of the common duct.[8]

EXPERIMENTAL METHODS

Mongrel dogs weighing from 15 to 17 Kg. were used in this work. With an animal under ether anesthesia, we tied the common bile duct with two silk sutures as closely as possible to the duodenal wall and cut the duct between the sutures. The head of a small mushroom catheter was fixed into the gallbladder by means of a purse-string suture, the free end of the catheter being brought out of the abdomen by means of a stab wound. The catheter was allowed to drain continuously into voluminous sterile dressings. Several days postoperatively, when the dog appeared and acted normally, the daily injection of from 3 to 6 cc. of ether into the catheter was begun. The only pressure exerted on the ether during the injections was that minimal amount necessary to expel the fluid from the glass syringes used for the instillations. Sterile technic was used at all times. While this method of injection was being studied, we noticed marked decreases in the total output of bile. After much difficulty, a satisfactory method was evolved for studying the output of bile, which at the same time permitted us to make the necessary injections. Here, too, the common duct was doubly tied and severed in the foregoing manner. For drainage we used a 10 cm. glass tube with a 1.5 cm. open bulb at each end. One bulbous tip was inserted into the gallbladder and held in place by a purse-string suture. The other end was brought to the outside by forcing it through a small stab wound in the wall of the right side of the abdomen. The external bulbous tip of the tube was sufficient to prevent it from being drawn into the abdomen by respiratory or other movements. The tubing within the abdomen was covered with omentum. To the external bulb of the drainage tube was attached one arm of a T tube, and to another arm of the T tube was connected a balloon for collecting the bile. A screw clamp on the remaining arm of the T tube converted the apparatus into a closed system, so that the biliary drainage was collected in the balloon. To empty the balloon the screw clamp was removed from the free arm of the T tube and placed on the arm connected to the glass drainage tube, thus enabling us to express the bile from the balloon without forcing the fluid back into the biliary tree. To instill the ether the clamp was then placed on the arm of the T tube connected to the balloon, and the drug could be injected through the open arm of the T tube into the gallbladder without entering the collecting bag. After the injection the clamp was replaced on the free arm of the T tube and the bile allowed to collect for another twenty-four hours. All of the external collecting apparatus was held in a circular enameled metal cup, which was in turn supported by a binder of stout canvas. Pockets, which exactly fitted the cups, were tailored into the binders, so that when the latter were tightened the edges of the cups made no undue pressure on the dog's abdomen. The whole apparatus was well tolerated by all the dogs and did not seem to interfere with their normal activity. The injections of ether were not started until a normal output of bile had been maintained for three days. Animals which did not fully recover from the operation or those showing any signs of infection were discarded. The usual diet of meat and water was not varied throughout the experiment. The dogs were taken from their cages each day for fifteen minutes of exercise. When an animal died or was killed because of poor condition, a postmortem examination was done, and sections for microscopic study were taken from various parts of the biliary tract and liver. Tissue was also taken from the pancreas, spleen and kidneys.

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[4] Vollisnieri, cited by Sherwood, K. K.: Historical Sketch of Cholelithiasis, Northwest Med. **30**:335-340 (July) 1931.

[5] Wright, G.: The Value of Turpentine in Gall-Stone Surgery, Brit. M. J. **2**:1808, 1908.

[6] Pribram, B. O.: Zur Beseitigung eingeklemmter Choledochuspapillensteine, Deutsche med. Wchnschr. **58**:1167-1169 (July 22) 1932.

[7] Pribram, B. O.: New Methods in Gall-Stone Surgery, Surg., Gynec. & Obst. **60**:55-64 (Jan.) 1935.

[8] We were unable to dissolve the most ordinary bilirubin calcium stones rapidly by mixing them with ether, as described by Pribram. The process usually took a period of days.

To determine the solubility of the usual stone in the biliary tract under conditions simulating incarceration within and blockage of the common bile duct, we placed various stones in pieces of rubber tubing so as to just block the lumen of the tube. The piece of tubing containing the stone was then connected to an inverted bottle partially filled with ether. In order to maintain atmospheric pressure within the bottle at all times, a glass U tube was also placed through the stopper with both arms above the level of fluid. The bottle was agitated daily so as to place "new" ether in contact with the stone.

EXPERIMENTAL RESULTS

Ether was injected into the biliary tract in eleven dogs, and in six of these the total daily output of bile was checked as described. All of the dogs objected strenuously to the injections. This reaction usually subsided in from two to four minutes but on several occasions was prolonged into what seemed to be a convulsive seizure. The increased pressure within the biliary tract, due to evaporation and movement, caused variable amounts of ether to be expelled. In the dogs with the closed system of biliary drainage, the screw clamp was never replaced on the free arm of the T tube until the ether was no longer being expelled. After the injection dressings were applied, and the animals were removed from the boards and allowed to walk. More often than not a dog would be unable to walk normally, assuming a drunken reeling gait. When this reaction occurred, the dog also became nauseated and vomited. This disturbance in walking usually lasted from ten to fifteen minutes, but the nausea and vomiting persisted for from one half to two hours. Once the injections began, all of the dogs became listless, had meager appetites, appeared extremely weak and lost weight.

All of the dogs (six) on which the twenty-four hour output of bile was measured showed a marked decrease after the instillation of ether. The normal output varied from 130 to 160 cc. per twenty-four hours. After only three or four instillations we could collect but 40 to 50 cc. a day. This decrease in the output of bile was progressive, so that in the three dogs which received the greatest number of injections (eight, eleven and fourteen) there was a complete stoppage of biliary secretion. The eight remaining animals either died or were in such poor condition that they were killed with ether before receiving as many as eight injections.

Clinical signs of jaundice were noted in three of the dogs. These were observed in animals which survived longest and which had also ceased to secrete bile.

At autopsy none of the animals had free bile in the peritoneal cavity, though in one a small amount of a blood-tinged serous fluid was found. Grossly the liver appeared normal except in the three dogs exhibiting jaundice. In these the liver was firmer and definitely bile stained on section. In two animals the bulbous tip of the glass tube which had been maintained in the gallbladder was found to be covered with a layer of fine concretions. In one the common bile duct was thought to be definitely thickened. No gross changes were noted in any other portion of the biliary tract or in any of the other abdominal or thoracic viscera.

Microscopically, the ether seemed to cause a progressive destruction of the mucosa lining the biliary tract and gallbladder. At first the columnar cells became edematous and pale staining and had much lighter nuclei than normally. The cytoplasm then became filled with small granules, the nuclei became still lighter staining and finally the cells appeared to disintegrate and slough. The microscopic changes in the liver were definite and in some instances marked but did not seem to be quantitatively related to the amount of ether injected. Likewise, the hepatic pathologic process gave no clue as to the amount of bile secreted nor as to the general condition of the animal.

The hepatic parenchymal cells were for the most part edematous, and the cytoplasm took an abnormally light stain. The nuclei seemed normal except in those cells which had undergone a fine granular degeneration. In these instances the nuclei were pale. In the dog which had received fourteen injections the liver showed scattered areas of complete destruction. All of the sections showed marked engorgement of the capillaries and slight thickening of the arterial walls. The Kupffer cells were numerous and contained phagocytosed granules, the latter being especially marked in the animals which were jaundiced. These microscopic changes in the liver were present diffusely throughout the lobule and did not seem to vary with proximity to the bile duct or blood vessel. The pathologic process was slightly more marked, however, in the sections taken at or near the hilus than in those taken from the periphery.

Sections of the spleen, pancreas and kidneys were normal in all dogs except one, which showed many hyaline casts in the renal tubules.

Attempts to dissolve stones placed in rubber tubing in the manner described were unsuccessful after fifteen days of constant contact with the ether. One stone was left in place for three months without leakage of ether past the site of incarceration and obstruction.

COMMENT

The most interesting and noteworthy result of these experiments was the rapid decline of the dogs immediately after the beginning of the injections of ether. The sudden decrease in the total output of bile can be accounted for only by injury to the liver parenchyma, it being conceded that the hepatic cell is the source of bile salt formation. This result, however, is not unusual, for Whipple and Smith[9] found that when small amounts of chloroform, another lipoid solvent, were administered by mouth a "marked depression in the bile salt output" resulted. Thus one would expect an even greater decrease in the total output of bile when, as in the present experiment, the toxic material came in direct and immediate contact with the liver parenchyma. That the injected ether actually did enter the hepatic biliary tree was deduced from the fact that from 3 to 5 cc. of a suspension of barium sulfate injected into the drainage tube was seen to spread up into the liver.

The convulsive seizures, rapid loss of weight and extreme listlessness of the animals point to another expected result, namely, a disturbance in glycogenesis, one of the major functions of the liver. King[10] called attention to the frequent reports of convulsions under ether anesthesia which have appeared in English literature since 1925. Sears[11] expressed the belief that this reaction is a result of hypoglycemia due to a depleted reserve of glycogen and has advocated as treatment the intravenous administration of concentrated solutions of dextrose. Evans, Tsai and Young,[12] working with cats, found that ether anesthesia lowers the glycogen content of the liver from 15 to 20 per cent in from five to six minutes, with a subsequent drop to less than 50 per cent in one hour, after which the fall is checked. Even though ether anesthesia is accompanied by hyperglycemia, which Cantarow and Gehret[13] stated they believed to be due to an increased hepatic glycogenolysis, Major and Bollman[14] found that prolonging such anesthesia caused a marked decrease in the skeletal glycogen. Unfortunately no studies on the chemistry of the blood or tissue glycogen were done in this work. Also interesting would have been a quantitative analysis of the amount of ether present in the various tissues and a comparison of the results with those of Gettler and Siegel,[15] who found that the ether in tissues is "always higher than 0.3 cc. in 500 Gm." in cases in which the patient died under full ether anesthesia or as the result of an accidental overdose. However, as explained previously, histologic evidence of damage due to ether in the spleen, pancreas or kidneys was entirely lacking except in one dog, which showed several hyaline casts within the kidney tubules.

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[9] Whipple, G. H., and Smith, H. P.: Bile Salt Metabolism: Liver Injury and Liver Stimulation, J. Biol. Chem. **89**:727-738 (Dec.) 1930.

[10] King, H. J.: Convulsions Under Ether Anesthesia, Am. J. Surg. **30**: 182-184 (Oct.) 1935.

[11] Sears, J. B.: Late Ether Convulsions: Report of Two Cases, J. A. M. A. **100**:1150-1152 (April 15) 1933.

[12] Evans, C. L.; Tsai, C., and Young, F. G.: Behaviour of Liver Glycogen in Experimental Animals; Methods: Effect of Ether and Amytal, J. Physiol. **73**: 67-80 (Sept.) 1931.

The development of jaundice in three of our dogs was in keeping with the same findings after the administration of other lipoid solvent hepatic toxins, such as chloroform and carbon tetrachloride. The cause of this jaundice, as suggested by Mann and Bollman,[16] "appears to be due in part to hepatic injury and in part to excessive formation of bilirubin which cannot all be eliminated by the injured liver." As mentioned before, the phagocytosis of the excess pigment by the Kupffer cells was especially marked in the jaundiced dogs.

Owing, no doubt, to the relatively short period of observation, sections of the liver failed to reveal other pathologic changes, such as fatty degeneration, cirrhosis or regeneration.

The essential pathologic changes in the extrahepatic biliary tract and the larger bile ducts in the liver were those of necrosis and sloughing of the epithelial lining. There was a noted absence of any inflammatory changes, with only an occasional submucous infiltration of small round cells. Here again the short period of observation precluded the possibility of regeneration of this destroyed mucosa. Under favorable conditions the epithelium lining the ducts is capable of regeneration,[17] and in cats Stewart and Lieber[18] found that ligation of the common duct caused an enormous proliferation of the mucosa of the larger ducts, particularly after the tenth day.

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[13] Cantarow, A., and Gehret, A. M.: Ether Hyperglycemia, with Especial Reference to Hepatic Disease, J. A. M. A. **96**:939-941 (March 21) 1931.

[14] Major, S. G., and Bollman, J. L.: Effect of Ether and Iso-Amyl-Ethyl Barbiturate (Amytal) Anesthesia on Glycogen Content of Skeletal Muscle, Proc. Soc. Exper. Biol. & Med. **29**:1109-1111 (June) 1932.

[15] Gettler, A. O., and Siegel, H.: Isolation of Ether from Human Tissues, Arch. Path. **17**:510-515 (April) 1934.

[16] Mann, F. C., and Bollman, J. L.: Jaundice: Review of Some Experimental Investigations, J. A. M. A. **104**:371-374 (Feb. 2) 1935.

[17] Halperin, G.: Regenerative Capacity of the Extrahepatic Biliary Tracts, Surg., Gynec. & Obst. **56**:868-883 (May) 1933.

[18] Stewart, H. L., and Lieber, M. M.: Ligation of Common Bile Duct in Cat, Arch. Path. **19**:34-36 (Jan.) 1935.

The almost immediate distress of the animals after the injection of the ether was due partially, we think, to the irritating character of the substance and probably more to the rise in pressure within the biliary tract resulting from the evaporation of the ether at body temperature. Pribram[6] warned against the injection of more than 2 to 3 cc. at a time, stating that larger quantities produced pain. Zollinger[19] distended the common duct in man by means of a balloon inserted during laparotomy and found that an increase of pressure within the duct led to severe pain, nausea, vomiting and respiratory difficulty. This description accurately portrays the condition of our animals soon after the instillation of ether. Sheldon,[20] when injecting skiodan into the common duct for visualization, noticed that the patient complained of precordial anginal pain when too great pressure was used.

The deposit of calcium on the glass tubes draining the gallbladder is an interesting but common finding. Hospers[21] cited several workers who before the turn of the century reported the deposition of calcium on foreign bodies placed within the gallbladder. This condition may have been due, as is frequently the case in calcification of the wall of the gallbladder,[22] to the mobilization of the calcium by the blood cells, present in this instance as a result of the operative procedures. A more plausible explanation, however, is that the deposition of calcium was due to the continued irritation of a foreign body, the glass tube in this case. Moynihan[23] gave particular credence to this factor in his work dealing with the deposition of a layer of calcium on gallstones. By making roentgenograms of operative specimens, he found that with few exceptions the smaller stones were translucent, but as a stone became larger a thin radiopaque layer of calcium formed on its surface. It was also his opinion that the calcium deposited more rapidly on an impacted stone.

This covering of calcium is, we think, the explanation of our inability to dissolve an apparently soluble stone by placing it in constant contact with ether as described before. Though solitary stones have been found to contain from 98 to 99 per cent cholesterol, the common mixed or combination gallstones were found to have an average cholesterol content of but 94 per cent.[24] Thus while the calcium content is relatively small, its position as an enveloping layer may easily be sufficient to prevent solution of the stones by lipoid solvents.

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[19] Zollinger, R.: Observations Following Distension of Gall-Bladder and Common Duct in Man, Proc. Soc. Exper. Biol. & Med. **30**:1260-1261 (June) 1933.

[20] Sheldon, L. B.: Clinical Study of Biliary Secretion in Case Presenting Completely Obstructed Common Duct, J. A. M. A. **104**:915-916 (March 16) 1935.

[21] Hospers, C. A.: Experimental Production of Gall-Stones, with Review of Literature, Arch. Path. **14**:66-78 (July) 1932.

[22] Davis, J. E., and Bookmyer, R. H.: Intramural Calcification of Gall-Bladder, Ann. Surg. **96**:413-417 (Sept.) 1932.

[23] Moynihan, B.: Mitchell Banks Memorial Lecture on Gallbladder and Its Infections, Brit. M. J. **1**:1-6 (Jan. 7) 1928.

Thus far we have discussed features concerning this method of treatment as brought to light by our experimental work. There are other points to bear in mind before injecting a lipoid solvent into the biliary tract. Ever since Graham[25] first described it, the occurrence of hepatitis has been accepted as a "constant accompaniment of cholecystitis." Since we also think of stones as evidence of an antecedent disturbance of the gallbladder or the liver,[26] in any case in which surgical intervention for stones is necessary there is, or has been, infection of the liver, and there may be a more dangerous reaction to a toxic agent than is expected or is desired.

Another theoretical consideration is the possibility of the ether causing pancreatitis. That this is commonly possible mechanically was demonstrated by Cameron and Noble[27] on postmortem experimentation. They inserted 3 mm. calculi into the terminal portion of the choledochus and raised the intraductal pressure to 100 mm. of water. It was found that fluid entered the pancreatic duct in sixty-six of one hundred cases, and in seventy-four of the one hundred there was an ampullary communication between the choledochus and the duct of Wirsung. They also called attention to the fact that during retching or vomiting the pressure within the common duct usually rose to 350 mm. of bile, but might go as high as 1,000 mm. These findings are in striking accord with those of Wangensteen and his co-workers,[28] who reported that in 69.8 per cent of their cases of acute pancreatitis the condition was associated with stones or disease of the gallbladder. Since in our experiment the common duct was severed just outside the duodenum, we were unable to check these findings.

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[24] Pickens, M.; Spanner, G. O., and Bauman, L.: Composition of Gall-Stones and Their Solubility in Dog Bile, J. Biol. Chem. **95**:505-507 (March) 1932.

[25] Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521-537 (May) 1918.

[26] Bortz, E. L.: Restoration of Biliary Function, M. J. & Rec. **136**:244-248 (Sept. 21) 1932.

[27] Cameron, A. L., and Noble, J. F.: Reflux of Bile up the Duct of Wirsung Caused by an Impacted Biliary Calculus, J. A. M. A. **82**:1410-1414 (May 3) 1924.

[28] Wangensteen, O. H.; Leven, N. L., and Manson, M. H.: Acute Pancreatitis (Pancreatic Necrosis): Experimental and Clinical Study, with Special Reference to Significance of Biliary Tract Factor, Arch. Surg. **23**:47-73 (July) 1931.

While the experimental evidence and conjectural possibilities offered here may present this method of treatment as a rather perilous one, it must be pointed out that our experimental procedures were not identical with the therapeutic ones advocated by Pribram. For example, we injected the ether into the gallbladder instead of into the choledochus. This probably permitted more ether to remain within the biliary tract. Likewise, our injections of ether were not followed by irrigations with sodium chlorate, which would remove some of the residual ether. Then, too, the amount of ether used in the dogs (from 3 to 6 cc.) was a relatively much larger dose than a similar amount in human beings. We might also mention that we made no effort to prolong the period of survival of the animals by the administration of carbohydrates, a much needed substance in cases of damage to the liver.

While these exceptions may explain the toxicologic toleration of this type of treatment by man, they do not account for Pribram's success in overcoming lithoid obstructions of the choledochus by lavage with ether. Of course, it is entirely possible that all of his cases were those in which the stones were composed of pure cholesterol or at least were not covered with a layer of calcium and were, therefore, readily dissolved by the ether. Then, too, the lavage may have been instrumental in overcoming spasms of the sphincter of Oddi, which may in contracture resist pressures much higher than either the secreting pressure of the liver or the expulsive pressure of the gallbladder.[29] A more likely explanation, however, is that the mechanical effects of the injections of ether, sodium chlorate or iodized oil were sufficient to dislodge and remove the cause of the occlusion. Frequent reports of similar experiences have appeared in the literature. For example, about twenty-five years ago Matas [30] was "surprised" by the rapid cure of biliary fistulas after catheterization of and injection of fluids into the biliary tract. Neuwirt,[31] after the injection of 15 cc. of iodized oil into a biliary fistula for visualization, discovered that stones were passed with the stool and via the fistula onto the abdominal wall. More recently, Hicken, Best and Hunt [32] summarized their experiences with the statement that "occasionally a lipoiodine [iodized oil] lavage of the common duct will flush out small stones or inspissated plugs of mucus which are causing distress and discomfort in cholecystectomized patients, or perhaps release the sphincterismus."

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[29] Ivy, A. C., and Bergh, G. S.: Applied Physiology of Extrahepatic Biliary Tract, J. A. M. A. **103**:1500-1504 (Nov. 17) 1934.

[30] Matas, R.: Catheterization of the Common Duct as a Practical and Effective Upper Route for Enteroclysis Medication in Toxic Biliary Cases (McArthur's Procedure), Surg., Gynec. & Obst. **12**:185-186, 1911.

[31] Neuwirt, K.: Therapeutische Wirkung einer Ölfüllung der Gallenwege, Zentralbl. f. Chir. **57**:1663-1665 (July 5) 1930.

[32] Hicken, N. F.; Best, R. R., and Hunt, H. B.: Cholangiography: Visualization of the Gallbladder and Bile Ducts During and After Operation, Ann. Surg. **103**:210-229 (Feb.) 1936.

In conclusion, we can recommend only as thorough as possible surgical removal of the stones in the common duct. If obstruction of the choledochus develops, an injection of the inert iodized oil may be of value not only in visualizing the biliary tract but in the release of the obstruction.

SUMMARY

A closed system for the collection of bile from, and the injection of materials into, the biliary tract is described.

The experimental and theoretical results of direct injection of ether into the biliary tract are discussed.

Attempts to dissolve the usual cholesterol stones in ether are described and dissolved.

Pribram's method is discussed.

CONCLUSIONS

Ether may be very toxic when injected directly into the biliary tract.

The thin layer of calcium so frequently present around a cholesterol stone will prevent the ready solution of the stone by ether.

Lavage of the biliary tract with iodized oil is suggested for removing obstructions of the common duct as well as for visualization.

CARCINOMA OF THE INFRAPAPILLARY PORTION OF THE DUODENUM

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The purpose of this communication is to report two new cases of carcinoma of the infrapapillary portion of the duodenum and to review and analyze the previously reported authentic cases of this condition. Of sixty-two cases reported, twenty-eight were regarded as satisfactory,[1] a clinical history and gross and microscopic descriptions of the tumor, obtained at laparotomy or at postmortem examination, being presented in each report. Eight [2] additional cases, although probably authentic examples of this condition, were not included because the reported data were insufficient for our purposes. Twenty-four cases [3] were discarded because the reports lacked a histologic description, and in two others [4] the exact situation of the tumor was uncertain.

The first reported example of a carcinoma of the infrapapillary portion of the duodenum is usually accredited to Chomel (1852), but the case described by Irwin in 1824 is probably a genuine example of this condition and should take precedence. Since the journal in which this paper was published is not readily accessible, a brief abstract is presented. The patient was extremely emaciated and complained of pain in the epigastrium, which was excruciating at times and was usually

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[1] Déscroizelle; Baillet; Rolleston; Fenwick; Schiewe; Syme; Thaysen; Head; Cade and Devic; Deaver and Ravdin; Vickers; Lundberg; Pommay and Seille; Pauchet and Luquet; Dewis and Morse (cases 7 and 12); Ylvisaker; Schofield; Forni; Meyer and Rosenberg (cases 3 and 4); Mateer and Hartman (case 6); Kellogg; Fariñas Mayo; Sala; Harries and Harrison (case 2); Eger (case 2); Laning and Loy (case 2), and Davis.

[2] Larkin; Geiser (case 7); Venot; Markus; Borrmann (case 3); Raiford (cases 44556 and 46153), and Price (case HB 7008).

[3] Irwin; Chomel; Williams; Markoe; Whittier (case 13); Herz; Geiser (cases 5, 6 and 8); Bland-Sutton; Erdmann; Crane (case 1); Eusterman, Berkman and Swan (cases 13, 14 and 15); Dewis and Morse (cases 10 and 11); Susman (case 3); Surmont and Tiprez; Rankin and Mayo; Eger (case 2); Lengemann; Joyce (case 8), and Auvynet.

[4] Bandelier (case 6) and Goldberg (case 2).

accompanied by vomiting of a green fluid from two to four hours after meals, obstinate constipation and black feces. About three weeks before death a large tumor was discovered in the right side of the hypochondrium; the prominence was present for from eight to ten days and then subsided. The autopsy report is as follows:

> On exposure of the abdominal cavity, the stomach was seen displaced in a singular manner, and enormously distended. This organ occupied almost the whole of the right hypochondrium—its great curvature extending down to the left iliac region. After its removal from the body, it was opened and its contents were found to amount to half a gallon of green bile, somewhat diluted with whiskey and water, which had been taken for common drink. It was then slit from one extremity to the other, carefully washed, and contrary to the opinion I had formed of its condition, not a vestige of disease was to be discovered in any part of this organ. The liver, also, was free from disease, but adherent on its posterior surface—gallbladder much distended with thin green bile. Having examined thus far without being able to detect the seat of the disease, our attention was directed to the duodenum, which was found much enlarged, and externally hard and unyielding. On exposing its cavity, it was found in a cancerous state, and closely studded with tubercles, varying in size from a hickory nut to that of a hazel nut. The largest of them contained matter resembling cream somewhat dried. The whole surface of the seat of ulceration presented a ragged, uneven, lacerated appearance. The quantity of pus found about the diseased part of the gut was upwards of a gill. Pancreas natural in regard to situation, but diminished to one half its usual size and scirrhous. On cutting into it, the interior presented much similarity in colour and texture to that of a boiled cow's udder. Duct natural. . . . The mesenteric glands enlarged—and between the lamina of the mesocolon were contained several tumours of about the size of a large pea, in a state approaching to scirrhous. . . .

The reports of two new cases of carcinoma of the infrapapillary portion of the duodenum follow:

REPORT OF CASES

Case 1.—R. R., a white man aged 52, was admitted to the Jefferson Hospital on Aug. 28, 1933, with a loss of 30 pounds (13.6 Kg.) in weight and persistent pain in the region of the gallbladder of two months' duration, which suddenly became excruciating two weeks previously. The pain appeared to originate in the right flank posteriorly and radiated along the right costal margin to the area of the gallbladder and occasionally to the region of the right scapula. It was unaffected by the ingestion of fried or fatty foods or sodium bicarbonate. There were associated belching, nausea, vomiting, hiccups and a feeling of fulness and discomfort in the right upper abdominal quadrant. Obstipation developed a week after the acute onset; the urine became dark, and the stools were either black or acholic. Jaundice was first noted by the examining physician. The liver was enlarged and tender, and the abdomen was somewhat distended and rigid on light palpation over the right upper quadrant. When the examiner's thumb was pressed under the right costal margin, the patient would catch his breath on deep inspiration.

Roentgenographic examination of the stomach and intestines was unsatisfactory. No gallbladder shadow was observed after the oral administration of a mixture of tetra-iodophenolphthalein sodium and tartaric acid. The urine contained albumin and bile pigments but no bile salts. The stools were acholic but later became dark and contained blood and sometimes fat. Repeated drainage of the biliary tract yielded little if any bile. Analysis of the gastric contents after a test meal showed a maximum total acidity of 113 at the end of thirty minutes and a maximum of free hydrochloric acid of 100 at the end of forty-five minutes; lactic acid and bile were absent, and blood was present in all specimens. The Kahn and Wassermann reactions of the blood serum were plus four. The red blood cell count dropped from 4,320,000 on the patient's admission to 2,300,000; the number of platelets increased steadily from 572,000 to 1,055,000. The nonprotein nitrogen content of the blood rose from 38.96 to 90.88 mg. per hundred cubic centimeters of blood; the creatinine content was 1.65 mg., and the cholesterol content, 156 mg. On his admission the reaction to the direct van den Bergh test was positive; the serum bilirubin was 4.2 mg., and 45 per cent of bromsulphalein was retained at the end of thirty minute periods (2 mg. dose). On the day that death occurred the van den Bergh reaction had not changed; the serum bilirubin was 17.45 mg., and 100 per cent of the bromsulphalein was retained. Death occurred on October 3.

Autopsy was performed thirteen hours after death. The combined gross anatomic and microscopic diagnoses were (1) adenocarcinoma of the duodenum, with extension to the pancreas and metastasis to the regional lymph nodes, liver and lungs; (2) hydrohepatosis with marked jaundice; (3) chronic aortitis; (4) arteriosclerosis of the coronary arteries; (5) fatty infiltration of the myocardium, and (6) calcified tuberculous lesions in the lungs.

The posterior wall of the duodenum presented a sharply defined firm round elevated lesion, 3.5 cm. in diameter, which involved the mucous membrane covering slightly more than half the circumference of the intestine. The proximal margin of the lesion occupied a position 13.5 cm. distal to the pylorus and 2.5 cm. beyond the papilla of Vater. The wall of the intestine in the area of involvement was composed of soft gray, homogeneous tissue. This tissue penetrated deeply into the pancreas and more superficially extended beneath the mucous membrane to the margin of the ampulla of Vater. Many of the regional lymph nodes were enlarged and replaced by soft gray, homogeneous tissue adherent to the pancreas and the duodenum. The proximal portion of the duodenum and the stomach and esophagus were markedly distended with fluid and gas. Several small shallow diverticuli were observed on the posterior wall of the duodenum just below the pylorus.

The papilla of Vater was thickened and indurated and appeared more prominent than usual. The ampulla received the duct of Wirsung and the common bile duct, both of which were obstructed. The duct of Santorini opened directly into the duodenum at a point slightly anterior to and 2.5 cm. above the papilla of Vater; it was large and appeared to be continuous with the main pancreatic duct within the body of the pancreas. All the biliary passages were markedly dilated and stained with bile. Obstruction of the biliary tract seemed to result from a combination of neoplastic infiltration of the wall of the ampulla of Vater and from external pressure of the tumor tissue in the duodenum and pancreas and the enlarged lymph nodes in the retroperitoneal space. The wall of the gallbladder was somewhat thickened, and the fundus extended several centimeters below the inferior border of the liver. The liver was enlarged, somewhat cystic and mottled dark green. On section there were innumerable sharply circumscribed gray tumor nodules scattered throughout the parenchyma, the largest of which measured from 4 to 6 cm. in diameter.

Microscopic sections of the duodenum passed through a large tumor nodule, the base of which rested on the muscular coat of the intestine (fig. 1). The epithelial cells extended downward from the mucosal nodule and spread out laterally into the submucosa and in one place penetrated deeply through the muscular wall into the subserous tissue. At the summit of the nodule the duodenal mucosa became atrophic and merged into atypical epithelial cells, loosely distributed and supported by a scant stroma, which formed the core of several tall, villus-like structures. The blood vessels of the stroma were often thin and immature. The atypical epithelial cells were round, oval or polyhedral, with smooth acidophilic or pale foamy cytoplasm. The nuclei were hyperchromatic or pale, vesicular, small or large, often crescentric, lobulated and eccentrically placed in the cell. As a rule they were single, but many individual cells contained from two to ten nuclei. There were a few bluish interlacing strands among these epithelial cells, suggesting the presence of mucin. Scattered through the nodule were a number of polymorphonuclear leukocytes, usually in association with necrotic areas, which were numerous in the sections. There were many collections of round cells and a few polymorphonuclear leukocytes in the deeper layers of the musculature. The metastatic lesions in the lung and liver resembled the primary nodule in the duodenum. There were several large neoplastic nodules lying in relation to some of the ducts in the pancreas, which showed a moderate degree of fibrosis about the smaller ducts. In this situation, as in the metastatic lesions of several of the lymph nodes, the atypical epithelial cells were paler; they tended to form better developed acini and contained more mucin than the primary duodenal nodule. Several areas of tumor tissue were observed in and about small thin-walled vessels outside the capsules of some of the lymph nodes.

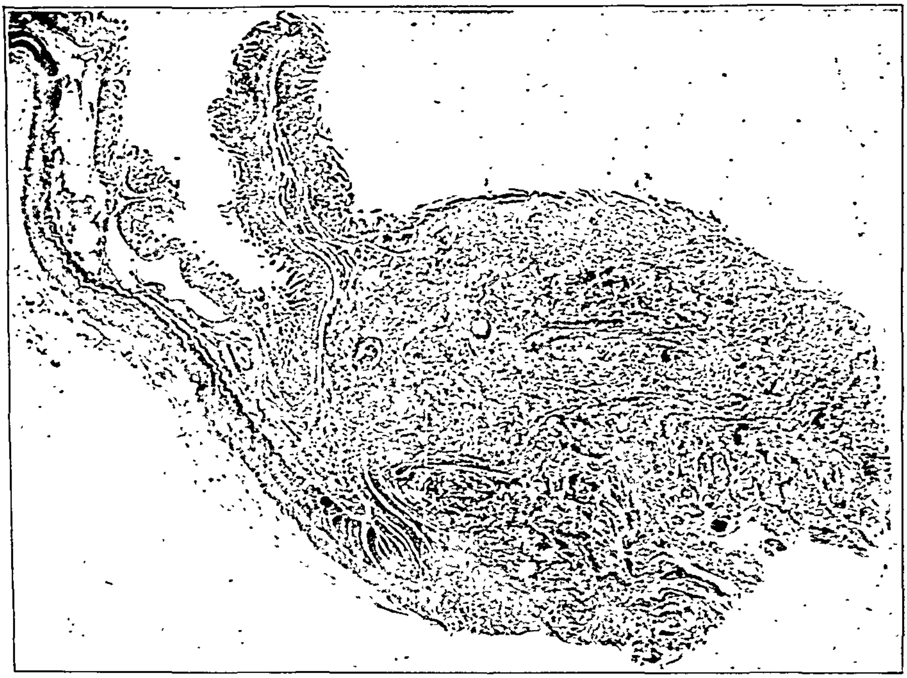

Fig. 1.—Microscopic section of the duodenum at the margin of the tumor, showing infiltration and destruction of all the coats of the intestine; circa × 7.

The hepatic parenchyma presented the characteristic picture of biliary stasis, with necrosis and pigmentation about the central veins, proliferation of the smaller bile ducts, marked perilobular fibrosis and round cell infiltration and a few lesions of biliary necrosis.

Case 2.—P. S., a Negress aged 51, under treatment for diabetes and hypertension of at least a year's duration, was admitted to the Philadelphia General Hospital on Oct. 23, 1933, with nausea, vomiting, abdominal pain, diarrhea and constipation. The onset occurred suddenly ten days previously, with steady epigastric pain, which became worse on eating, and diarrhea. This was succeeded by obstinate constipation and vomiting of clear liquid and recently ingested food. On physical examination the skin was dry, and the breath smelled of acetone. Three liters of foul-smelling fluid was siphoned off through a stomach tube. Roentgenographic examination of the gastro-intestinal tract after the ingestion of a barium sulfate meal disclosed a dilated, atonic stomach, which had a persistent filling defect on the greater curvature of the pylorus. The duodenal cap was well outlined and seemed perfect, but beyond this point little barium sulfate was observed to pass, which gave a slightly granular appearance to the remainder of the duodenum. The lower portion of the intestinal canal seemed normal after a barium enema. There was no anemia; the chloride content of the blood was 584 mg. per hundred cubic centimeters; the sugar content varied between 130 and 234 mg., and the Kahn reaction of the blood serum was negative. The urine contained a faint trace of albumin and had a specific gravity of from 1.015 to 1.039.

At laparotomy, on November 11, a firm nodular constriction was found which was thought to be a tumor of the pylorus, and gastro-enterostomy was performed for relief of obstruction. On the sixth postoperative day a suppurative lesion developed in the right parotid gland, which was incised and drained on November 20. A sinus tract formed and later ruptured into the right external auditory canal, resulting in paralysis of the right side of the face. The patient died on December 9 from an infection of the blood stream.

Autopsy was performed nine hours after death. The combined gross anatomic and histologic diagnoses were: (1) adenocarcinoma of the infrapapillary portion of the duodenum, with extension to the pancreas and metastasis to the liver; (2) marked dilatation of the proximal portion of the duodenum; (3) a patent gastro-enterostomy opening; (4) abscesses of the right parotid gland and kidney; (5) arteriosclerosis of the aorta and the renal, coronary and pancreaticoduodenal arteries; (6) acute degeneration of the myocardium and renal tubular epithelium; (7) congestion of the lungs, spleen and liver; (8) interstitial fibrosis of the pancreas, and (9) fatty change of the liver.

About 11 cm. from the pylorus the duodenum presented an annular constriction 3 cm. in diameter, with a lumen which barely permitted the passage of a fine probe. The wall of the duodenum at the point of involvement was composed of firm white tissue, which infiltrated the head of the pancreas. The proximal portion of the duodenum was markedly dilated. The common bile duct was patent, slightly thickened and measured 1.5 cm. in diameter; bile could be expressed through the ampulla of Vater, which lay 1 cm. proximal to the duodenal lesion. No metastatic nodules were observed in the abdominal lymph nodes.

Microscopic sections through the lesion included the duodenum and an adjacent portion of the pancreas (fig. 2). The strip of mucous membrane terminated abruptly at either end and did not show a transition laterally into malignant tissue. In the deeper layers of the mucosa and muscularis mucosa were several nodules of atypical cells with pink cytoplasm and hyperchromatic nuclei, frequently with large multiple lobulations and numerous mitotic figures. The cells around the periphery of these nodules tended to form columnar rows resembling the cells in the depths of the duodenal crypts. The entire submucosa was invaded by nests and strands of tall columnar vacuolated cells, which occasionally formed elongated acini and closely packed cellular nests. They penetrated through the muscular coats into the septums of the pancreas for a short distance. The stroma was moderate in amount and infiltrated with small round cells.

The liver showed metastatic lesions, acute congestion, central lobular cytoplastic vacuolation and a moderate degree of periportal round cell infiltration. The kidney was intensely congested and contained a focus of early suppuration in the medulla.

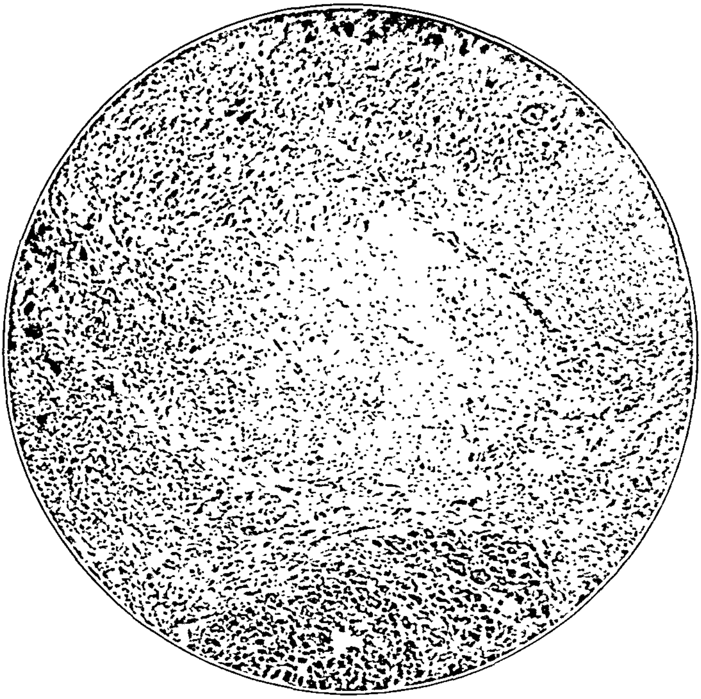

Fig. 2.—Microscopic section of the wall of the duodenum just beneath the ulcerated area. There were atypical epithelial cells in the submucosa, which permeated through the muscular coats into the septums of a small portion of the pancreas attached to the deeper portion of the section; × 40.

AGE AND SEX; INCIDENCE

In the series of cases studied the patients consisted of twenty men ranging in age from 40 to 74 years, with an average age of 58.2 years, and ten women (two Negresses) ranging in age from 35 to 61 years, with an average age of 48.3 years.

Carcinoma arising in the duodenum is estimated to be found in from 0.01 to 0.1 per cent of all postmortem examinations. The percentages commonly given range from 0.01 to 0.03 (Eusterman and Balfour). Nearly one half of the malignant growths of the small intestine are said to develop in the duodenum (Kellogg), but these statistics are based on reports in the literature, and many of these are not authentic cases. Of the two new cases here reported, one was found at the Jefferson Medical College Hospital in a series of 3,526 autopsies and the other at the Philadelphia General Hospital in a series of 20,176 autopsies performed since 1920.

ANATOMY

Textbooks on anatomy usually state that the duodenum is divided into the following parts: (1) the superior portion, from 3 to 5 cm. in length, which commences at the pylorus and passes upward and backward, where it forms, with the second portion, the superior flexure; (2) the descending or vertical portion, from 8 to 12 cm. in length, which receives the bile and pancreatic ducts and forms with the third portion the inferior flexure; (3) the inferior portion, which is again subdivided into (*a*) the horizontal portion, from 8.5 to 10 cm. in length, which terminates in (*b*) the ascending portion, from 3 to 7 cm. in length, this in turn terminating in the duodenojejunal flexure.

Any division of the duodenum which fails to take into consideration the point of entrance of the bile and pancreatic ducts is inadequate for clinical purposes. Embryologically, all of the duodenum above the papilla of Vater is developed from the foregut, and the remainder of the small intestine is derived from the yolk sac, or so-called midgut. With the papilla of Vater as an orientating mark for subdivision, that portion of the duodenum above is the suprapapillary segment; that below, the infrapapillary segment.

The infrapapillary portion extends from the papilla of Vater to the duodenojejunal junction. It consists of three subdivisions, which are best seen in the U-shaped duodenum, less well in the C-shaped type and not at all in the V form: 1. The descending portions extend along the right side of the vertebral column from the papilla of Vater to the inferior angle on a level with the upper border of the body of the fourth lumbar vertebra. It is in relation in front with the transverse colon and small intestine and behind with the right kidney in the neighborhood of the hilus, the renal vessels, the inferior vena cava and the psoas muscle. At its medial side are the head of the pancreas and the common bile duct and laterally the right colic flexure. 2. The horizontal portion, from 5 to 7.5 cm. long, begins at the inferior angle, passes from right to left, with a slight inclination upward in front of the great vessels and crura of the diaphragm, and ends in the ascending portion in front of the aorta. It is crossed by the superior mesenteric vessels and the mesentery. Its posterior surface lies on the right crus of the diaphragm, the inferior vena cava and the aorta, and the upper surface is in relation with the head of the pancreas. 3. The ascending portion, 2.5 cm. long, extends along the left side of the aorta as far upward as the level of the superior border of the second lumbar vertebra, where it turns abruptly forward to end in the duodenojejunal flexure. It lies in front of the left psoas muscle and left renal vessels.

MORBID ANATOMY

The dimensions of the primary tumor in the duodenum were stated in twenty-five cases. In a little over half of these it measured from 3 to 5 cm. in length, in six cases from 1 to 2.5 cm. and in five cases from 6 to 8 cm. In Rolleston's case the infrapapillary segment was involved in its entirety. A circumscribed tumor 4 cm. or less in diameter was localized just beyond the papilla of Vater in eight cases and at or near the duodenojejunal flexure in thirteen. In eight cases the proximal margin of the growth was situated near the papilla of Vater, and the distal margin of the neoplasm did not extend beyond the horizontal portion of the duodenum, except in the extensive growth considered previously. Ulceration was present in sixteen cases. A few ulcers were crater-like, measuring upward of 6 cm. in diameter, with margins variously described as hard, resistant, cicatrized, indurated, friable, rolled or elevated. A gaping artery was present in the floor of one ulcer, and perforation occurred in four.

The primary tumor was completely annular in nineteen cases and was confined to the posterior or the median wall or to both in six. Some degree of stenosis was present in all cases, being complete or almost complete in seventeen. The annular tumors were frequently fixed and consisted of compact grayish white cicatricial-like tissue. The non-annular growths were polypoid or pedunculated and usually soft in consistency.

Proximal to the primary duodenal lesion, the alimentary canal was regularly dilated well up into the esophagus. The proximal portion of the duodenum was frequently distended in a funnel-shaped or pyriform manner, and its mucous membrane was flattened and atrophied or occasionally puckered and thrown into folds, while the muscular coats were usually attenuated but occasionally were thick and hypertrophied. The pyloric sphincter showed marked thinning, and the orifice was dilated, sometimes to a diameter of 12 cm., the stomach and duodenum together often appearing as a bilocular viscus. The gastric contents occasionally measured 1,500 cc. and consisted of degenerated blood and remnants of food. In Schiewe's case the stomach was the size of a "pig's bladder," with the pylorus in the right anterior axillary line and the duodenum the width of a normal colon. Fenwick stated that the anterior abdominal cavity of his subject was chiefly occupied by two thin-walled sacs lying side by side; the one on the left consisted of a dilated stomach, while the other, which was ovoid and 8 inches (20 cm.) in length with a maximum circumference of 13 inches (33 cm.), represented the upper two thirds of the duodenum. In occasional cases in which the clinical manifestations indicate low grade, long-continued obstruction, the wall of the stomach and proximal portion of the duodenum may become markedly hypertrophied. Rolleston explained this change on the basis that from time to time food collects proximal to the obstruction and, by forcing the duodenum downward, leads to complete closure of this fixed and already strictured portion of the bowel.

Metastases or extension of the primary tumor to adjacent structures occurred in fifteen cases. Metastatic deposits were present in the lymph nodes in ten, in the liver in seven and in the lungs in two. The regional nodes were involved in all ten cases of lymphatic metastases, the mesenteric nodes in four, the retroperitoneal nodes in three and the periportal nodes in three, while in one case practically all the visible nodes in the abdomen and pelvis were affected. Adhesions to the surrounding structures were encountered in half the cases, but which of these were neoplastic could not be accurately estimated. Neoplastic extensions into the pancreas occurred in five cases, and into the surrounding fat, posterior abdominal wall and aorta, in one each. The largest tumorous deposits in the pancreas did not exceed 3 cm. in diameter. The primary and infiltrating tumors together with the cancerous lymph nodes and adhesions sometimes produced a large fixed neoplastic mass, which compressed surrounding tissues and viscera. Obstruction of the terminal end of the common bile duct or the ampulla of Vater occurred in five cases, due in most instances to extension of the primary neoplasm.

Perforation of the duodenum occurred in four cases. Rupture developed spontaneously in Dewis and Morse's case 12, and the resulting lesion was walled off by surrounding tissues. In Pommay and Seille's case, fistulous formation occurred three days after gastroenterostomy and biopsy and resulted in diffuse peritonitis. In Schofield's case perforation occurred after the implantation of radon seeds, which were believed to have interfered with healing of the duodenostomy wound. Perforation in Ylvisaker's case was found fifteen days after incision and drainage of the pancreas and several months after high voltage roentgen therapy over the epigastric region.

Morbid anatomic lesions other than the foregoing were mentioned only rarely. Chronic pancreatitis was observed in six cases, suppurative pancreatitis in one and obstruction of the duct in Wirsung in two. Of five cases in which biliary stasis was present, the hepatic changes were described in one and resembled those resulting from biliary obstruction due to other causes. Chronic cholecystitis was found in two cases, suppurative cholangeitis in one, pyemia in two and biliary calculi in one. Degenerative changes in the tubular epithelium of the kidney were frequently noted. Inflammatory hyperplasia of the lymph nodes in the upper part of the abdomen was regularly associated with extensive infection in and about the primary duodenal neoplasm.

HISTOLOGIC PICTURE

The lesion was designated as a glandular carcinoma in all cases, but aside from this statement microscopic data were scanty. Biopsy material or the entire surgical specimen was obtained for examination by laparotomy in nine cases. The growth was of the scirrhous type in seven cases, the medullary type in four and the mixed scirrhous and medullary type in two. Papillary formations were marked in five cases, and variable amounts of mucin were present in four; in two of these the formation was described as a mucinous adenocarcinoma. Variations from a well differentiated carcinoma of the intestinal type with cylindric cells to one of rather marked anaplasia were described, and in ten cases anaplasia and rapid cellular division were noted. Inflammatory changes were regularly present in the connective tissue stroma and were pronounced in three cases in which ulceration was present.

PATHOLOGIC PHYSIOLOGY

There are relatively few studies of the abnormal physiologic changes associated with clinical obstruction of the infrapapillary segment of the duodenum. In animals, Elman and Hartman concluded that the principal cause of death is a change in the chemical constituents of the blood, resulting primarily from the loss of gastro-intestinal secretions and secondarily from circulatory and renal insufficiency due to dehydration. By introducing a solution of sodium chloride below the point of obstruction, life can be maintained in experimental animals, whereas the reintroduction of bile and pancreatic juices fails (Armour, Brown, Dunlop, Mitchell, Searls and Stewart). Owing to the similarity between the toxic reaction of the material from obstructed loops of bowel and that of histamine, Dragstedt suggested that the latter was formed by the bacterial decomposition of histidine as the result of stasis. He expressed the belief that histamine accelerates the secretogogic action of the intestines and that the excessive secretion in turn facilitates distention and consequent breakdown of the normal resistance of the intestinal mucosa against toxic material in the lumen of the bowel. It is also probable that death is hastened by slow absorption of histamine-like substances, which are believed to accelerate chemical changes occurring as a result of loss of gastric secretion (Andrus, Guest, Gates and Ashley).

From a clinical point of view the signs and symptoms of obstruction of the type considered in this paper have been divided by Rivers and Thiessen into two groups. In the first are included symptoms arising from local mechanical disturbances or those incident to neoplastic invasion of surrounding tissues. The second group includes systemic disturbances arising as a part of the toxemia associated with obstruction together with the manifestations of malignant cachexia, metastasis and extension. On the basis of previous studies it has been shown that the symptoms resulting from interference with normal peristalsis are flatulence, nausea and regurgitation of food, which may not reach their maximal intensity for an hour or more after eating. Vomiting of the retention type develops, even with incomplete obstruction, and leads to varying degrees of malnutrition and dehydration. At first the stenosis is adequately counteracted by increased peristalsis, but later compensation becomes inadequate, and signs and symptoms of partial or complete obstruction may supervene rapidly. Obstruction by malignant disease is rarely intermittent, and relief is seldom obtained except by surgical measures. Since the lesion is situated below the ampulla of Vater, the vomitus or gastric contents obtained by lavage usually contain bile in liberal amounts, except in occasional instances in which the biliary passages as well as the intestine are obstructed.

CLINICAL FEATURES

Onset.—The onset of the condition was acute in twelve cases, gradual throughout in twelve and first gradual and then acute in six. A history of antecedent illness was elicited in three cases in which the onset was acute and in seven cases in which the course was gradual throughout.

The duration of the condition in eleven cases in which the onset was acute ranged from fourteen days to seven months, averaging slightly less than four months. In one case the patient was not traced after operation and discharge from the hospital. The initial symptoms in this group consisted of epigastric distress or pain (twelve cases), vomiting (ten), loss of weight and strength and anorexia (five), a sense of abdominal weight or pressure (two), belching (two) and constipation, diarrhea, abdominal distention, hiccups and bulimia (one each). Later manifestations included constipation (four), loss of weight and strength and anorexia (four), and jaundice, vomiting, a sense of weight or pressure in the abdomen and abdominal distention (one each).

The duration of the condition in cases in which the course was gradual throughout ranged from five to nineteen months, averaging slightly less than eleven months in nine instances; the ultimate fate of three patients was not stated. Initial symptoms in this group consisted of pain (six cases), vomiting (five), loss of weight and strength (two), abdominal distention (two) and a sense of weight or pressure in the abdomen, belching and diarrhea (one each). Later manifestations were loss of strength and weight and anorexia (eight cases), pain (four), vomiting (four), diarrhea (three), abdominal distention (two) and a sense of weight or pressure in the abdomen and constipation (one each).

In the group in which the course was at first gradual and then acute, the duration of the first stage was approximately ten months and of the second, approximately four and a half months, the average total duration being about eleven months. The gradually developing symptoms included pain (three cases), a sense of weight or abdominal pressure (one) and loss of weight and strength (one). The subsequent acute manifestations were vomiting (five cases) and flatulence, jaundice, abdominal distention, constipation and loss of weight and strength (one each). Still later, there were loss of weight and strength and anorexia (two cases), constipation (two) and pain, jaundice and abdominal distention (one each).

The clinical diagnoses in the cases in which there was an antecedent history were reported as lead poisoning, cholecystitis, neurosyphilis, traumatic rupture of the intestine and arteriosclerosis with diabetes and with hypertension (one case each) and simple ulcer (two). In the remaining three cases the patients complained of symptoms referable to the upper part of the abdomen which were not diagnosed.

Pain.—Pain was present in all but one case and was usually severe and sometimes colicky or cramplike. It was frequently intermittent at first, then increased markedly in severity and eventually became continuous. In a few cases there was simply epigastric distress, slight burning or a feeling of distention and fulness. Pain occurred with the onset in twenty-two cases and later in seven. It was situated in the epigastrium in twenty-one cases, in the right upper abdominal quadrant in three, in the lower part of the abdomen in two and in the right flank posteriorly in one. Radiation to the back occurred in four cases and to the region of the shoulders in two. This symptom occurred from one half to two hours after meals or was aggravated or intensified by food in seventeen cases, while in three cases it was unaffected by food. Relief sometimes followed the ingestion of food, vomiting or lying on the right side, and in one case both pain and meteorism disappeared after the administration of morphine. Attacks of severe pain were sometimes followed by epigastric burning, discomfort and a sense of weight in the abdomen and in one case these were preceded by hunger and followed by vomiting. There was associated tenderness in eight cases and abdominal rigidity in two.

Vomiting.—Vomiting was present in twenty-five cases, absent in four and not mentioned in one. It appeared with the onset in seventeen and after the onset in eight, usually occurring from a few minutes to several hours after meals. It was at first intermittent and tended to become incessant terminally and was only occasionally associated with nausea. The vomitus was frankly bilious in ten cases, and in three contained coffee-ground material; sometimes food ingested from several hours to several days previously was present, in which case the vomitus often had a foul odor due to putrefactive changes. Some patients had gastric succorrhea, and the amount of fluid vomited exceeded that ingested; in Rolleston's case 11 pints (6.2 liters) was vomited in fifteen hours, and in Fenwick's case 13 ounces (0.4 liter) of bilious fluid was obtained from the stomach, which had been emptied and without food since the previous night. Vomiting occurred at any time of the day or night and was not associated with any particular kind of food. Sometimes, however, the patients vomited at regular intervals, as, for example, after meals, once a day or periodically every second day. Of the four cases in which vomiting was absent (Deaver and Ravdin; Pommay and Seille; Pauchet and Luquet, and Ylvisaker), the primary lesion was ulcerated in all, markedly obstructive in only one, perforated in two, annular in two and fungating in one, and there was dilatation of the proximal duodenal segment in three. Similar anatomic conditions were present in other cases in which vomiting was a marked symptom.

The vomitus or material removed for gastric analysis in twenty cases revealed the presence of bile in fourteen and blood in seven. The absence of bile from the vomitus in two cases can be attributed to the development of complete biliary obstruction. Free hydrochloric acid was absent in eight of fourteen specimens, and in one of these the reaction was alkaline. In the remaining six specimens the free hydrochloric acid varied from 5 to 100. The total acidity varied from 9 to 100 in nine specimens; being above 40 in 6. In Laning and Loy's case, in which the gastric contents were analyzed after the injection of histamine, the free hydrochloric acid and total acidity were unaffected in all specimens.

Jaundice.—Jaundice developed in three cases relatively late in the course. In Schofield's case the proximal margin of the growth encroached on the ampulla of Vater. In Meyer and Rosenberg's case 3 the primary tumor consisted of a large constricting mass just below the papilla of Vater, and there was marked dilatation of the biliary and pancreatic ducts and suppurative cholangeitis. In our case 1 the proximal margin of the tumor was 2.5 cm. distal to the papilla of Vater and had extended proximally beneath the mucosa into the wall of the ampulla; the bile and the pancreatic ducts were further compressed by masses of tumor tissue in the duodenum, pancreas and retroperitoneal lymph nodes. The late development of jaundice is consistent with the observations made at autopsy in that obstruction to the extrahepatic biliary passages occurs relatively late from extension and metastasis to the pancreas, surrounding tissues and regional lymph nodes and exceptionally, in part, from the pressure of a large primary cancer. Of interest in this connection is the statement by Rivers and Thiessen that the appearance of icterus with obstructive lesions of the infrapapillary portion of the duodenum is an almost certain indication of malignancy.

Morbid conditions tending to cause biliary obstruction and jaundice were present in incipient form in several other cases. In Rolleston's case the tumor had reached the biliary papilla, and the common bile duct was dilated as a result of beginning obstruction. In Schiewe's case, although the papilla of Vater was encircled by neoplastic tissue, there was no apparent biliary obstruction and no jaundice. Similarly, in Dewis and Morse's case 7 and in our case 2 the common bile duct was slightly dilated, but jaundice was not yet apparent. Gallstones played no part in the production of jaundice, being present in only one instance and then in the gallbladder. Of the five cases in which there was partial or complete biliary obstruction, bile was detected in the gastric contents in two, was absent in one and was not mentioned in two.

Constipation and Diarrhea.—Constipation or obstipation was reported in nine cases, occasionally in association with roentgenographic evidence of stasis in the colon. Diarrhea occurred in five cases, as a transitory manifestation at the onset in two and in association with lead poisoning in another. So-called pancreatic diarrhea was reported only once. The stools of one patient were acholic, while those of two others, with bilious vomiting and tight strictures of the infrapapillary portion of the duodenum, contained bile. One patient with jaundice had stools which were dark because of the presence of blood.

Other Laboratory Data.—Patients with carcinoma of the infrapapillary portion of the duodenum tend to have marked anemia and slight leukocytosis, especially during the cachectic phase. Of nine cases in which it was possible to estimate the color index, it was high (from 0.9 to 1.1). An abrupt decrease in red blood cells was a terminal feature associated with loss of blood in the vomitus and stools. Evidences of impairment of hepatic and renal function were present in our case, with obstructive jaundice. Marked nitrogen retention occurred in one case, with incessant vomiting, nephrosis and an extreme degree of duodenal obstruction. The results of urinalysis were reported in eighteen cases; in ten the urine was said to be normal; albumin was present in six, bile in three, indican in one and diminished amounts of chlorides and increased quantities of creatine in one.

Roentgenographic Studies.—Roentgenograms of the gastro-intestinal tract were taken after a barium meal in eighteen cases; in three the studies were unsatisfactory. In the others the findings were so varied that a brief analysis of each case seems warranted.

There were six cases in which the lesion was fairly well localized. In Pauchet and Luquet's case the barium did not pass beyond the fourth segment of the duodenum, the third portion being markedly dilated and having the appearance of the stomach. Anatomically, there was an ulcerated constricting lesion near the duodenojejunal junction. In Mateer and Hartman's case there were a filling defect in the third portion of the duodenum and stasis of barium in the proximal segments and stomach; at autopsy a large ulcerated lesion was found 4 cm. below the papilla of Vater. In Farinas Mayo's cases there were ptosis and distention of the stomach and dilatation of the duodenum up to its junction with the jejunum. Fluoroscopic examination showed active peristaltic and antiperistaltic movements, the barium being carried to the duodenojejunal angle; at the end of six hours almost the entire barium meal was still retained in the duodenum, which was maximally distended. Anatomically, there was a completely stenotic annular lesion at the duodenojejunal angle. In Lundberg's case the wide open pylorus was recognized, and the duodenum was well filled and very wide in its lower portion; strong peristalsis and successive contractions of the circular muscles were seen here, and the lumen was still filled after four hours. Autopsy disclosed a completely annular lesion at the duodenojejunal junction. In Sala's case there were dilatation and stasis of the duodenal cap and stasis and deformity of the descending portion of the duodenum, which was interpreted as being due to external pressure by a pancreatic tumor. Autopsy revealed an ulcer of the infrapapillary portion 5 cm. in diameter, extensive local adhesions and masses of cancerous lymph nodes; the pancreas, however, appeared to be normal. In Kellogg's case the gastric retention noted clinically was attributed roentgenographically to adhesions involving the second and the fourth duodenal segment; at autopsy an almost totally obstructive lesion was found near the terminal end of the duodenum.

There were five cases in which the roentgenographic picture suggested the presence of a lesion at or near the pylorus. In Deaver and Ravdin's case a roentgenographic diagnosis was made of adhesions or ulcer near the pylorus, the duodenum being reported as probably normal; at autopsy an ulcerated tumor was situated below the papilla of Vater.

In Vicker's case the column of barium was obstructed just beyond the pylorus, the stomach being huge and atonic; at laparotomy the tumor was found in the region of the duodenojejunal flexure. In Forni's case the duodenal bulb was partially filled with barium, but there was none in the remainder of the duodenum; at autopsy an annular almost totally obstructive lesion the size of a hen's egg was found in the third portion of the duodenum. In Harries and Harrison's case a filling defect of the pylorus was observed, with marked dilatation of the stomach, and a diagnosis of carcinoma of the pylorus was made; at laparotomy the neoplasm was found at the duodenojejunal flexure. In our second case a filling defect was observed at the pylorus, and at autopsy an annular stenosing cancer was found 11 cm. beyond the pyloric ring.

No suggestion of a lesion was observed roentgenographically in four cases, even though the morbid anatomic changes were striking. In Meyer and Rosenberg's case 3 there was marked obstruction by a fungoid mass, 5 by 6.5 cm., just below the papilla of Vater. In Davis' case there was a practically annular lesion, measuring 3.3 cm. in diameter, near the terminal end of the duodenum. In Laning and Loy's case the third portion of the duodenum was practically completely stenosed by an ulcerating mass 5 cm. long. The roentgenographic examination in Head's case was made seven months before death, and at autopsy the lumen of the intestine was almost completely occluded by a large cauliflower-like growth.

From an analysis of these data it is apparent that the accuracy of roentgenographic diagnosis in six cases is somewhat offset by the fact that in five the lesion was localized incorrectly at or near the pylorus and in four others no lesion could be demonstrated.

PHYSICAL EXAMINATION

A mass was palpated in the region of the primary tumor in five patients, and a doubtful or suggestive mass was felt in two. The mass was movable in three cases, moved with the respirations in one and was associated with tenderness in three and with rigidity in one. Tenderness was elicited in six other cases in which masses were not palpable, in two of which there was associated abdominal rigidity. In Schiewe's case marked pulsations were transmitted through a palpable tumor mass, which at autopsy was found to be adherent to a locally stenotic aorta. The presence or absence of a palpable mass was correlated with the size of the local tumor together with the associated inflammatory and neoplastic lesions; it was found that many large anatomic specimens were not detected during life, yet in one case an exceedingly small primary tumor was palpated. Conditions other than the primary tumor were occasionally noted on palpation. For example, palpation of the liver and gallbladder gave evidence of biliary stasis, and metastatic lesions on the liver and in the deep and superficial lymph nodes were noted. Dilatation of the stomach, sometimes to the iliac crest, was noted in eight cases, often with visible peristalsis and a succusion splash, which Fenwick heard below the navel and laterally in the anterior axillary line.

DIAGNOSIS

The diagnosis of carcinoma of the stomach was made in ten cases, in six of which the growth was believed to involve the pyloric region. In twelve cases the following diagnoses were made: carcinoma of the small intestine, obstruction of the small intestine, pyloric obstruction, pyloric stenosis from ulcer, retroperitoneal tumor, carcinoma of the head of the pancreas, duodenal or jejunal stenosis, duodenal ulcer with carcinoma superimposed and organic obstruction at the duodenojejunal flexure.

A correct diagnosis was made at laparotomy in thirteen of twenty-one cases, and in three no diagnosis was recorded. The diagnoses made in five cases were: carcinoma of the small intestine, a mass of doubtful nature in the third portion of the duodenum, hypertrophy of the pyloric sphincter, retroperitoneal sarcoma and carcinoma of the pylorus. One patient was twice subjected to laparotomy, and a mistaken diagnosis of hypertrophied pylorus was made on each occasion.

TREATMENT

The treatment of carcinoma of the infrapapillary portion of the duodenum has been either symptomatic or palliative or directed toward cure. Rational therapy for definitely obstructive lesions has been outlined by Rivers and Thiessen with a view of combating the toxemia in preparation for operation. Radiation therapy was employed in two cases (Ylvisaker and Schofield). Laparotomy was performed in twenty-one cases, and the procedures and results are presented in the accompanying table. The results were unsatisfactory in seventeen cases, and the ultimate fate of the patients in the remaining four cases was not determined, two of them being alive three months after operation, one of whom had extensive metastases. Schofield's case is of particular interest in view of his original method of treatment. First he performed biopsy, cholecystoduodenostomy and posterior gastro-enterostomy and six weeks later reopened the duodenum and implanted radon seeds directly into the tumor. A duodenal fistula developed, and the patient died on the twenty-ninth postoperative day, but no evidence of neoplastic tissue could be detected at this time, the tumor evidently being quite radiosensitive.

A review of the morbid anatomic data in the present series of cases indicates the difficulties which may be encountered in carrying out surgical treatment. There was extension or metastasis or both in fifteen cases—in ten to regional lymph nodes, in five to the pancreas, in one each to the posterior abdominal wall, surrounding fat and aorta and in approximately five to the ampulla of Vater and the common bile duct. Since these figures are based on routine autopsy, biopsy and surgical examination, it is probable that the true incidence of extension and

Results of Operation in Twenty-One Cases of Carcinoma of the Infrapapillary Portion of the Duodenum

Date	Authors	Operative Procedures	Period of Survival	Cause of Death
1904	Syme	Resection and end to end anastomosis	Alive 3 mo. later	
1917	Thaysen	Gastro-enterostomy	Died several days later	Hemorrhage
1919	Cade and Devic	Gastro-enterostomy	Died 36 hr. later	
1920	Deaver and Ravdin	Gastro-enterostomy	Died 2 hr. later	Shock
1924	Vickers	Gastro-enterostomy	Died 2 mo. later	
1924	Lundberg	Sept. ?: operation for traumatic rupture of intestine; Nov. 4: resection and end to end anastomosis	Alive 3 mo. later	
1925	Pommay and Seille	Gastro-enterostomy	Died 4 days later	Perforation and peritonitis
1927	Pauchet and Luquet	Resection		
1928	Dewis and Morse (case 7)	March 26: gastro-enterostomy; April 9: relief of obstruction due to kinking of bowel	Died 2 days later	
1929	Ylvisaker	Incision and drainage of pancreas	Died 15 days later	Hemorrhage
1930	Kellogg	Gastro-enterostomy	Died 8 days later	
1930	Schofield	April 16: cholecystoduodenostomy and gastro-enterostomy; May 28: radon seeds implanted	Died 29 days later	
1931	Meyer and Rosenberg (case 4)	Gastro-enterostomy and surgical ligation of duodenum	Died several weeks later	
1931	Forni	July 1930: exploratory; July 1931: gastro-enterostomy	Died about 3 mo. later	
1932	Mateer and Hartman	April: cholecystostomy; July: exploratory	Died 12 days later	Hemorrhage and shock
1934	Farinas Mayo	Resection		
1935	Davis	Resection and end to end anastomosis	Died 7 days later	
1935	Harries and Harrison	Resection and end to end anastomosis	Died 3 mo. later	
1935	Laning and Loy	March 15: cholecystostomy; March 25: gastro-enterostomy	Died 11 days later	Myocardial failure
1935	Sala	Exploratory	Died 5 days later	
1936	Author's case 2	Nov. 11: gastro-enterostomy; Nov. 17: incision of parotid abscess	Died 3 days later	Suppurative parotitis and pyemia

metastasis is much higher. Obviously all these factors must be taken into consideration in determining the therapeutic measures to be employed in individual cases.

SUMMARY AND CONCLUSIONS

A clinical and pathologic study is presented of thirty cases of carcinoma of the infrapapillary portion of the duodenum—two new cases and twenty-eight selected from the literature.

One of the new cases was found in 3,526 autopsies and the other in 20,176 autopsies.

Sixty-six per cent of the patients were men and 33 per cent were women; the average age was 58.2 years for the men and 48.3 years for the women.

The clinical onset was acute in 40 per cent of cases, with an average duration of four months; it was gradual throughout in 40 per cent, with an average duration of eleven months, and first gradual and then acute in 20 per cent, with an average duration of ten months, the gradual phase occupying four and a half months. The principal symptoms and signs irrespective of the mode of onset were pain, vomiting and cachexia. Other less common symptoms included anorexia, constipation, diarrhea, abdominal distention and jaundice. The vomitus or gastric contents were analyzed in twenty cases, and bile was detected in 70 per cent of these and blood in 35 per cent; free hydrochloric acid was absent in 57 per cent of fourteen specimens. A mass in the region of the primary tumor was palpated clinically in 16.6 per cent of the cases.

A correct preoperative clinical diagnosis is rarely made. An obstructing lesion of the duodenum was visualized roentgenographically with a fair degree of accuracy in 40 per cent of fifteen cases; in 33 per cent the lesion was incorrectly localized at or near the pylorus, and in the remainder no lesion was demonstrated. A correct diagnosis was made at laparotomy in 61.9 per cent of twenty-one cases, the results being unsatisfactory in 81 per cent of these, and the postoperative follow-up studies were incomplete in the remainder.

The primary tumor measured from 3 to 5 cm. in length in the majority of cases, and in one case the infrapapillary segment of the duodenum was involved diffusely in its entirety. All the tumors were of the glandular carcinomatous variety. The descending and ascending portions of the infrapapillary segment were most frequently involved. Extension of the primary tumor to adjacent structures and organs and metastases or both occurred in 50 per cent of cases. Some degree of obstruction of the terminal end of the common bile duct or of the ampulla of Vater or both occurred as a terminal feature in 16.6 per cent. Duodenal fistulas existed in 13.3 per cent. A high grade of intestinal obstruction was present in 56.6 per cent. The alimentary canal proximal to the primary duodenal lesion was maximally distended, the stomach and proximal portion of the duodenum often giving the appearance of a bilocular viscus.

In dealing with duodenal cancer clinically or pathologically, the papilla of Vater is the most important anatomic landmark in this region.

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EXPERIMENTAL PEPTIC ULCER PRODUCED BY CINCHOPHEN

METHODS OF PRODUCTION, THE EFFECT OF A MECHANICAL IRRITANT AND THE LIFE HISTORY OF THE ULCER

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Cinchophen has been used since 1911 in the treatment of gout. Toxic cirrhosis of the liver has developed in a few cases after its use. In attempting to produce hepatic damage experimentally in dogs, Churchill and Van Wagoner[1] in 1931 noted peptic ulcer in many of their animals. This and subsequent work by these investigators suggested to us that we attempt to produce peptic ulcer by the administration of cinchophen. Ulceration developed readily in dogs after the administration of this drug. This led to a consideration experimentally of (1) the genesis and healing process of this type of ulcer, (2) the effect of a mechanical irritant and (3) the possibility of producing ulcer by the administration of cinchophen other than by the oral route.

REVIEW OF THE LITERATURE

Experimentally, the methods for the production of acute peptic ulcer have been many and relatively simple, while, on the other hand, the methods for the production of chronic peptic ulceration have been few and relatively difficult.

Churchill and Van Wagoner[1] (1931), in attempting to produce hepatic damage by the administration of cinchophen, noted from one to three gastric ulcers occurring in five of six dogs. The same authors[2] (1932) noted peptic ulcer in nineteen of twenty-four dogs which received cinchophen. The drug was mixed with the diet in amounts varying from the dose for man to twenty-seven times that amount. The earliest ulcers developed in eight and ten days. In 90 per cent of the animals the ulcers were situated in the gastric pathway and were generally multiple. Ulcer of the first portion of the duodenum developed in four animals. The major symptoms noted were anorexia, occasional nausea and vomiting, tarry stools and loss of weight.

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Churchill and Manshardt[3] (1933) injected cinchophen in cottonseed oil into the jejunum daily and noted gastric ulcer in three dogs. They concluded that the ulceration was not attributable to a direct, local, toxic action of the drug on the gastric mucosa.

Shoji[4] (1933), using sixty rabbits and fifty dogs, gave doses of cinchophen varying from 0.1 to 0.2 Gm. per kilogram of body weight enterally and parenterally for from one to seven hundred days. Catarrhal inflammation and erosion were noted in the rabbits' stomachs, and ulcers formed in the dogs' stomachs.

Barbour and Fisk[5] (1933), who studied hepatic damage in dogs after the repeated oral administration of cinchophen, noted gastric ulcer in some of their animals.

Hanke[6] (1934), seeking an explanation for the origin of the ulceration that follows the administration of cinchophen, gave a series of cats large subcutaneous doses of a cinchophen preparation. Grossly the stomachs showed linear defects throughout the mucosa, and in many instances acute erosions and ulcerations were present. There were microscopic changes in the cells throughout the stomachs, but the greatest destruction was in the peptic cells.

Schwartz and Simonds[7] (1935) gave cinchophen in oil orally to cats, rabbits and guinea-pigs. Superficial erosions and ulcerations were noted in the stomachs of the cats, but ulceration was not found in the stomachs of the rabbits or of the guinea-pigs.

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Bollman and Mann[8] (1935) fed 1 Gm. of cinchophen to normal dogs five days a week. They noted peptic ulcer as early as the first week and as late as the fourteenth month.

No cases have been reported in which undisputed peptic ulcer due to cinchophen affected man. Reah[9] (1932) reported a case in which a patient died after therapy with cinchophen. Necropsy revealed a cirrhotic liver and a gastric ulcer. Bloch and Rosenberg[10] (1934) suggested the possible etiologic relationship of the cinchophen. They[11] reported a similar case in which necropsy revealed hepatic damage, multiple gastric ulcers and chronic gastritis.

METHOD OF INVESTIGATION

Seventy-seven dogs with an average range of weight varying from 8 to 17 Kg. were used in these studies. Each dog was normal before the experiments were begun. All normal dogs can be considered not to have peptic ulcer, as statistics have shown that it is rarely if ever present. The animals were given the routine kennel care, and the majority were fed a diet composed of cracker crumbs, ground horse meat and evaporated skimmed milk. The diet consisted of a calculated weighed amount known to be sufficient to meet the caloric requirement of the dog and will henceforth be called the "regular diet." A few dogs were given the regular kennel diet for contrast. This is a coarser meal consisting of dog biscuits and a cooked mash.

All surgical procedures were performed with the dogs under surgical narcosis induced by ether, and careful aseptic technic was employed. All dogs that were killed were given a light ether anesthesia and were then bled from the femoral arteries. These and the dogs that died were examined thoroughly. The handling and fixation of the specimens were considered extremely important. The stomach was carefully opened along the greater curvature on the anterior wall. At no time was any portion that was to be sectioned washed or wiped. The entire organ was stretched out and pinned to a piece of stiff cardboard; it was then fixed in a diluted solution of formaldehyde U. S. P. (1:10) for forty-eight hours or more. Multiple sections of all the organs were also fixed in a similar solution. All ulcers and multiple blocks of tissue removed from scattered regions throughout the stomach and duodenum were embedded in paraffin. These were sectioned semiserially and stained with hematoxylin and eosin.

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THE INCIDENCE OF PEPTIC ULCERS DUE TO CINCHOPHEN AND THE EFFECT OF A MECHANICAL IRRITANT

Physical agents which traumatize the gastric mucosa have been thought to be an etiologic factor in peptic ulcer. Fauley and Ivy[12] (1930) found that coarse particles remain in the stomach longer than do fine particles. Obviously, the coarse particles produce prolonged motor activity of the stomach and an increase of trauma to an acute lesion of the mucosa. These investigators have produced chronic lesions from acute ulcers and have prolonged the healing time of acute lesions by feeding mechanical irritants.

Walker[13] (1931) removed a portion of gastric mucosa from the stomach of several rabbits. A persistent mechanical irritant formed by a suture line directly beneath the lesion delayed the healing and increased the development of chronic ulceration.

Mann and others have demonstrated the presence of a mechanical factor in the production of peptic ulcer.

Our experiments on this phase of the subject follow:

Methods.—Fifty-one dogs were used in this study. These were divided into three groups. Group 1 consisted of twenty-eight dogs with an average weight of approximately 16 Kg. Twelve of them were fed the regular diet, and sixteen were fed this diet plus 100 Gm. of coarsely ground bone. The bone was given to determine the effect of mechanical irritation on the production and healing of the peptic ulcer. Regardless of the dog's size or weight, 2 Gm. of cinchophen well mixed with the diet was given daily to all animals. This is approximately three times the maximal daily dose for man and a fifth of the minimal lethal dose for dogs.

Clinically, the diagnosis of ulcer depended on the following symptoms: (1) vomiting of small amounts of gastric contents, (2) a tarry diarrhea of variable, but increasing severity, (3) anorexia, (4) anemia and (5) loss of weight and activity. If death did not occur at this stage from perforation of the ulcer, an exploratory operation was usually done and the presence of an ulcer confirmed.

Group 2 consisted of twenty dogs with an average weight of approximately 9 Kg. All were fed the kennel diet and were given 1 Gm. of cinchophen mixed with the meal daily five days a week. No drug was given the last two days of each week. It was intended in this way to determine the effect of the prolonged administration of a small dose of cinchophen. In every case the drug was given until the dog died or was killed.

Group 3 consisted of thirteen dogs. These were used as controls and did not receive any cinchophen. Three were fed the regular diet plus bone, and ten were fed the kennel diet. They were killed and examined after a longer period of observation than were any of the animals which received cinchophen.

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[12] Fauley, G. B., and Ivy, A. C.: Experimental Gastric Ulcer: The Effect of the Consistency of the Diet on Healing, Arch. Int. Med. **46**:524-532 (Sept.) 1930.

[13] Walker, M. A.: Healing of Gastric Mucous Membrane in Rabbits After Its Surgical Removal, Arch. Path. **12**:85-89 (July) 1931.

Results.—GROUP 1.—Peptic ulcer developed in twenty-seven (96.4 per cent) of this group of twenty-eight animals. No animal was given cinchophen longer than sixty consecutive days. The one dog which did not have an ulcer did not reveal any noticeable effect of the drug.

Of the twenty-seven dogs which had an ulcer, nine (32.1 per cent) had multiple ulcers, and eighteen (64.3 per cent) had a single ulcer. All were gastric ulcers. Two (7.1 per cent) of the dogs had an associated duodenal ulcer. Twenty-five (89.3 per cent) had a pyloric ulcer situated from 2 to 3 cm. from the pyloric ring on the posterior wall and lesser curvature of the stomach (fig. 6). No ulcer was seen on the greater curvature. Frequently small contact ulcers were found about a large chronic ulcer. The multiple ulcerations were spread over the entire gastric mucosa but were most marked in the pyloric and fundic regions.

In the sixteen dogs that were fed bone, ulcer developed clinically in an average of seven days after the administration of 14 Gm. of cinchophen. Ulcer developed in eleven of the twelve dogs that were not fed bone in an average of eighteen days after the administration of 36 Gm. of cinchophen. The incidence of perforation was slightly higher, although not significantly so, among the animals which were fed bone. There were seven (43.7 per cent) perforations among the latter animals, as compared with four (33 per cent) among the animals that did not receive bone.

The condition of all animals at the time of necropsy was good; little alteration was observed in the nutritional state. In many instances the dog gained weight. Where there was a loss of weight, it was relatively insignificant, usually being from 0.5 to 1.2 Kg.

Roentgenographic studies were attempted for diagnostic purposes, but the difficulties encountered did not warrant the continuance of such studies. Roentgenoscopic examination of five dogs in this group revealed the presence of an ulcer in four of them. Exploratory operation revealed the presence of an ulcer in all of the five dogs.

GROUP 2.—Peptic ulcer developed in nineteen of the twenty dogs in this group (animals given 1 Gm. of cinchophen five days a week). The dog which did not have an ulcer received 281 Gm. of cinchophen in four hundred and eighteen days. This dog gained 5 Kg. and showed no noticeable effect of the drug. The animals in this group received an average total dose of 198 Gm. of cinchophen in two hundred and seventy days. The smallest dose was 22 Gm. in thirty days and the largest was 423 Gm. in six hundred and thirty days. Four of the dogs gained weight, but there was an average loss of 0.35 Kg.

Seven (35 per cent) of the nineteen dogs had multiple ulcers, and twelve animals (60 per cent) had a single ulcer. In every case there was a gastric lesion, although two dogs (10 per cent) had an associated duodenal ulcer. In seventeen instances (85 per cent) a chronic ulcer was situated in the pyloric region, on the posterior wall and the lesser curvature of the stomach. One animal (5 per cent) had an ulcer on the anterior wall of the stomach near the lesser curvature. No ulceration was observed on the greater curvature. Perforation occurred in two (10 per cent) of the dogs.

The time of development of the ulcers was variable. In two dogs exploration was done six months after administration was commenced, but no lesion was noted; six months later an ulcer was found in each animal. An ulcer was found in other animals on the twenty-second, sixty-first and one-hundredth day after administration of the drug, but one animal did not have symptoms until the six hundredth day.

Group 3.—The thirteen control dogs which did not receive the drug were normal in every respect. There was no macroscopic or microscopic lesion of the gastric mucosa of the three dogs which received bone in their diet.

Comment.—These studies demonstrate that the oral administration of cinchophen will produce peptic ulcer in nearly 100 per cent of all dogs. It seems logical that the presence of any mechanical irritant, such as bone, might cause microscopic damage to the mucosa, thus making it susceptible to early damage by cinchophen; or that the drug might cause the original injury and the trauma produced by the bone might aid in the development of the ulcer and production of early symptoms. The latter is more probable, because in no case were we able to demonstrate microscopic damage of the mucosa when cinchophen was not given.

No reason can be given for the failure of peptic ulcer to develop in two of the dogs.

That the general nutritional condition of the dogs was not responsible for the development of ulcer is significantly shown by the following findings: 1. Ulcer occurred in many dogs before any alteration in the nutritional state could be observed. 2. Many of the dogs gained weight; when there was a loss of weight, it was relatively insignificant.

It is interesting to note that perforated ulcer was less frequent in the animals which received doses of 1 Gm. of cinchophen than in animals which received larger amounts of the drug. This suggests that the smaller doses of the drug do not inhibit the healing processes as much as do the larger amounts.

A comparison of the situation of ulceration in man with that in animals is of interest. From 10 to 40 per cent of the peptic ulcers which affect man are multiple. From 70 to 95 per cent of the gastric ulcers which affect man are situated along the *Magenstrasse* in the pyloric region. These facts were found true of the ulcers which developed in the dogs. However, the number of gastric ulcers after the administration of cinchophen as compared to the number of duodenal ulcers is in exact reversal of the situation of peptic ulcer as seen in man. This is possibly attributable to the fact that the gastric mucosa of animals appears to be more affected by toxins than does the duodenal mucosa. The duodenal ulcers in the animals were in a situation comparable to that of the usual duodenal ulcer in man. Ulceration of the greater curvature is rarely seen in human beings, and it was not observed in the dogs.

THE EFFECT OF CINCHOPHEN WHEN ADMINISTERED OTHER WAYS THAN ORALLY

We have mentioned that peptic ulcer has been produced by the administration of cinchophen directly into the jejunum and parenterally. We administered cinchophen rectally, intravenously and subcutaneously and by injection into an intestinal fistula to determine whether or not an ulcer would develop in the same manner as it did when the drug was given orally.

Injection into Intestinal Fistula.—Four dogs with an average weight of 15 Kg. and low jejunal or high ileal fistulas were used. Approximately 2 Gm. of cinchophen suspended in cottonseed oil was instilled daily through a catheter directly into the jejunum or ileum. Gastric ulcer, and in one instance, an associated duodenal ulcer, occurred in all four animals. The average time required for development of the ulcer was twelve days. There was no injury at the site of the injection of the drug.

Rectal Administration.—Two dogs weighing 19 Kg. were given a daily colonic irrigation; 4 Gm. of cinchophen in cottonseed oil then was instilled into the rectum. The animals showed symptoms referable to the action of the drug and were killed at the end of five days after the administration of the drug. Multiple acute gastric ulcers were found in both dogs. There was no injury to the rectum.

Parenteral Administration.—A neutral solution of the sodium salt of cinchophen was prepared for intravenous use. Each of two dogs, which weighed 18 Kg., was given an initial dose of 0.1 Gm. This was increased daily until a maximal dose of 2 Gm. had been reached. Definite symptoms were noted when a dose of 0.5 Gm. was given. These symptoms became progressively more severe as the dose of the drug was increased.

Immediately after the injection of 2 Gm. of the drug there were an increase in the nasal secretions, an increase in both the depth and the rate of respiration and an associated slowing of the beat of the heart. These symptoms were occasionally accompanied by involuntary micturition, forceful defecation and nausea and vomiting and rarely by a clonic twitching of the muscles. Fifteen minutes after the drug was given the symptoms disappeared, but the dogs remained stuporous for three hours. The most severe symptoms always occurred during the first hour. After the three hour period the animals appeared well and would eat as usual.

A more prolonged and a more gradual effect was desired; therefore, a daily subcutaneous injection of 2 Gm. of cinchophen suspended in cottonseed oil was substituted for intravenous administration. When the drug was thus administered, some symptoms were present by the end of the first hour. These reached their peak within three hours and gradually subsided during the next twelve hours.

Symptoms of ulcer developed in both dogs in one week. One dog was killed, and multiple acute gastric ulcers were present. The administration of cinchophen to the second dog was continued for an additional week. The dog was then killed. Two large subacute ulcers were found in the pyloric region on the lesser curvature and posterior wall of the stomach. There was an associated diffuse gastritis.

Two other dogs were given cinchophen intravenously for a period of less than one week. These were killed after one or two tarry stools had been passed. Microscopic lesions were found in the stomach of each dog.

THE DEVELOPMENT OF ULCER IN FUNDIC POUCHES

Method.—Fundic pouches were made in five dogs with an average weight of 11.5 Kg. This was done by cutting away a portion of the greater curvature of the stomach, forming it into a pouch and allowing it to drain through a de Pezzer catheter into a balloon which was carried at the side of the dog. These pouches were made primarily for a study of the gastric secretion, but in this paper mention will be made only of the results in regard to formation of ulcer.

Daily doses of cinchophen, which varied from 0.25 to 2 Gm., were mixed with the diet. The dogs were killed when they showed marked symptoms from administration of the drug or when the studies of the gastric secretion had been terminated.

Results.—Within four hours after 2 Gm. of cinchophen had been given orally, a small amount of macroscopic blood was present in the secretion in the pouch. The bleeding increased until the seventh hour. At this time the content of the pouch was cherry red. From the eighth to the twelfth hour after the oral administration of the drug, there was a rapid decrease in the amount of bleeding. Between the twelfth and the twenty-fourth hour, the secretion in the pouch was again clear. This same sequence occurred after each daily dose of cinchophen. The bleeding became progressively more severe, until at the time of definite formation of an ulcer there was some bleeding most of the time, but from the fourth to the twelfth hour after administration of the drug there was actually a hemorrhage. The amount of bleeding varied directly with the amount of drug given. The smallest dose of cinchophen that would produce an ulcer (0.5 Gm.) was the smallest dose that caused bleeding.

Ulceration developed in the pouches of all five dogs (fig. 1). Usually multiple, acute to subacute perforating lesions were found. In three animals the ulcer perforated the wall of the pouch. The other two had a microscopically perforating ulcer but were killed too early for gross perforation to occur. Ulcer formed in the pouch in from two to five days when the dose of cinchophen was 1 Gm. or more daily.

The stomachs in all five dogs were relatively free from injury, although superficial ulceration was noted at the lower end of the healed suture line (fig. 1) in four of the five dogs. There were also a few scattered linear erosions and mild gastritis. In no instance, however, was there a definite chronic ulcer in the stomach.

To determine whether or not cinchophen was being secreted into the isolated gastric pouches, several quarts of the secretion obtained from the pouches of dogs which were receiving cinchophen by mouth was concentrated by prolonged evaporation. This mixture was then subjected to a colorimetric test sensitive for cinchophen in amounts of from 0.01 to 0.1 Gm. A positive reaction was not obtained.

One quart of a mixture of the content of the pouch, which was not evaporated, was mixed with the diet of a dog which weighed 11 Kg. This was done daily for two weeks, and the stomach was then examined at necropsy. Ulceration was not found.

Comment.—These studies demonstrate that the administration of cinchophen by routes other than the mouth is equally effective in the production of peptic ulcer. They conclusively prove that the action of the drug is not local but occurs after absorption.

The rapidity with which symptoms appeared and then disappeared after the intravenous administration of the drug and the rapidity with which bleeding occurred in the fundic pouch and then as quickly subsided suggest that cinchophen is rapidly absorbed and rapidly excreted or destroyed. It is probable that the toxic effects and the excretion of the drug were nearly complete twelve hours after administration and were entirely complete after twenty-four hours.

The fact that acute ulcer occurred rapidly and was always of the perforating type in the fundic pouch lends support to the acid factor as an important element in the production of the ulcer. The drainage of the pouch was never complete; no alkalinizing mechanism was present, and at most times there was some free acid in the contents. The stomach of each dog showed little injury. It seems likely that once the original mucosal destruction had occurred, the constant presence of the free acid in the pouch increased the rate of formation of ulcer.

The negative results obtained with the colorimetric test and the failure to produce ulcer by feeding the contents of the pouch to a dog suggest that cinchophen as such is not secreted by the gastric mucosa. It is possible that it may have been present in an amount too small to detect with the method at hand or that it was present in a chemically changed form.

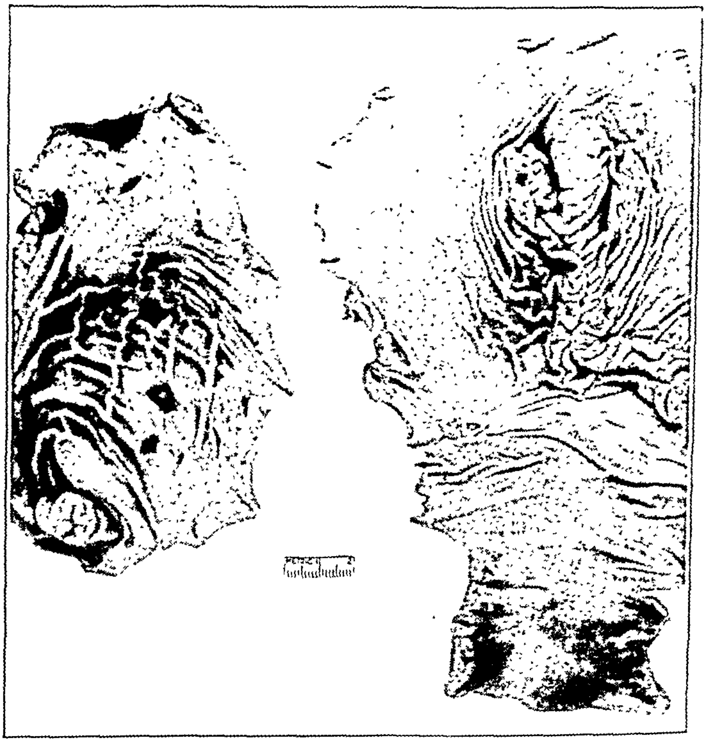

Fig. 1.—Fundic pouch and stomach. Three acute ulcers and one subacute perforated (center) ulcer are seen in the pouch; in the stomach there is an erosion of the lower tip of the healed suture line.

THE PATHOLOGIC STRUCTURE OF THE PEPTIC ULCER PRODUCED BY CINCHOPHEN

Van Wagoner and Churchill (1932) described the early ulcer due to cinchophen. They noted a destruction of the mucosa in the depth of a crypt. The mucosal cells were necrotic and covered with a layer of fibrin and polymorphic leukocytes. Radiating from the ulcer into the underlying tissue was an acute inflammatory reaction.

It is most frequently stated that peptic ulcer in man begins as a series of diffusely scattered acute ulcers. These tend to heal, and those in which the reparative process is less than the destructive process become chronic.

Mann[14] (1925) observed the healing process in experimental peptic ulcers. He noted that there is first a clearing of the base of the ulcer and then the formation of a granulation tissue bud, which tends to fill the crater. At the same time there is a subsidence of the inflammatory reaction and a proliferation of the connective tissue. The mucosa then grows in from the edge and covers the granulation tissue as a single layer of epithelium. This layer rapidly becomes polypoid, and finally there is an atypical epithelium on a base of scar tissue.

Caylor[15] (1926 and 1927) and Bliss[16] (1932) reported a similar process in the healing of peptic ulcer in man.

Our experiments on this phase of the subject follow:

Methods.—Three dogs with an average weight of 17 Kg. were given 2 Gm. of cinchophen daily in a regular diet. Regardless of the presence or absence of symptoms, they were killed at intervals of five days. Multiple sections were taken from various regions of the stomach and duodenum. These were stained and studied microscopically for the presence of the early lesion.

In addition to these three dogs, all of the animals previously mentioned were used in this study. The diets and the doses of cinchophen which were administered have already been described. Each lesion was studied grossly and microscopically. To obtain the healing ulcer, exploratory laparotomy was performed; the presence of an ulcer was definitely confirmed, and its size and situation was determined. The administration of cinchophen was stopped on the day of the exploration. Postoperatively the dog was fed his previous diet without the drug. The animals were killed at definite periods, which varied from three days to twelve weeks after administration of the drug had been commenced. The specimens were treated and sectioned as described previously.

Results.—All of the specimens obtained from the animals used in this study were examined macroscopically and microscopically. These animals had received cinchophen in variable doses for variable periods of time. This afforded an opportunity for the study of the various stages in the development and the healing of ulcer. We have summarized these results and present them as a composite general picture.

The Early Lesion: Each dog that had had one or more tarry stools had a lesion of the gastric mucosa. A diffuse gastritis was usually present after the third or fourth dose of 2 Gm. of cinchophen (fig. 2). The entire stomach was somewhat edematous and hemorrhagic in appearance. The mucosa was covered with an excess of mucus. Beneath this mucus and scattered over the entire mucosa, but chiefly throughout the fundic and pyloric regions, was an adherent layer of black altered blood. This appeared as a covering or as isolated pinpoint clots. Many of the clots were covered by folds of mucosa.

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[14] Mann, F. C.: Production and Healing of Peptic Ulcer, Minnesota Med. **8**:638-640 (Oct.) 1925.

[15] Caylor, H. D.: The Healing of Gastric Ulcer in Man, Ann. Surg. **83**:350-356 (March) 1926; The Healing Process of Gastric Ulcer in Man, ibid. **86**:905-917 (Dec.) 1927.

[16] Bliss, T. L.: Healing of Chronic Duodenal Ulcers, Am. J. Surg. **15**:93-98 (Jan.) 1932.

Multiple fine linear erosions were seen scattered between these blood clots. If a blood clot was removed, it was found that it filled one of these erosions. Occasionally there were superficial clean-appearing punched-out mucosal ulcerations. These usually were situated along the lesser curvature and varied from 1 mm. to 1 cm. in diameter.

Microscopically, sections through the area of gastritis demonstrated regions in which there were several necrotic mucosal cells sloughing into the lumen of the stomach (fig. 3). These were surrounded by a superficial inflammatory reaction, which consisted chiefly of polymorphonuclear leukocytes and involved only the mucosa. In many instances a bleeding mucosal blood vessel was noted. Throughout the stomach there were edema of the mucosa, a congestion of the mucosal blood vessels and an increase in the cellular elements, particularly of the round cells.

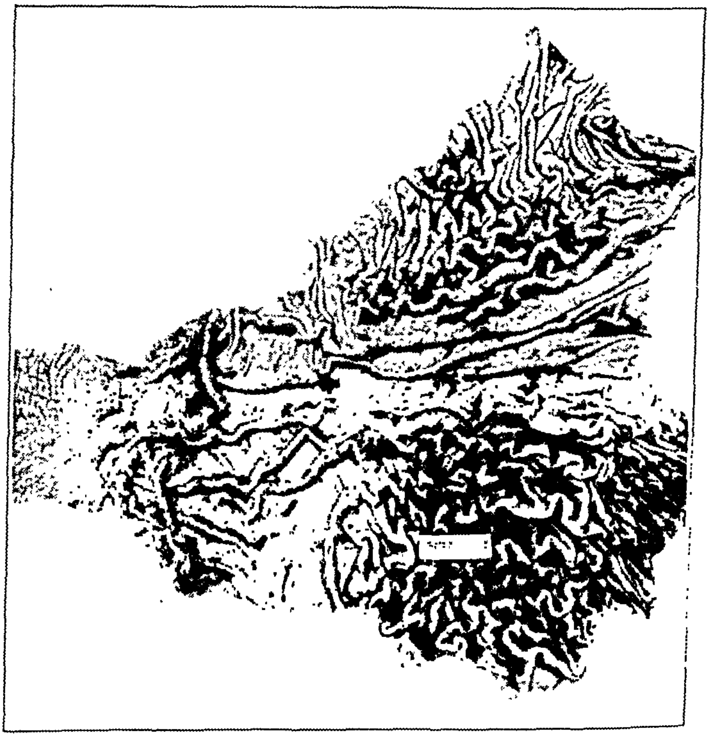

Fig. 2.—A specimen showing diffuse gastritis. An edematous mucosa, with multiple adherent blood clots, a few linear erosions and small ulcerations are seen.

In the majority of instances the erosions rapidly developed into acute peptic ulcers. If a dog was killed during this acute ulcerative stage, from thirty to sixty acute gastric ulcers were found (fig. 4). These ulcers had a fresh and punched-out appearance. The edges were cleancut, smooth and not edematous. The floor of each ulcer was usually smooth, firm and clean but at times was covered by a thin layer of blood. No granulation or pus was seen on the surface of an ulcer. The size of the ulcers varied from 2 mm. to 1 cm. in diameter. The acute ulcers

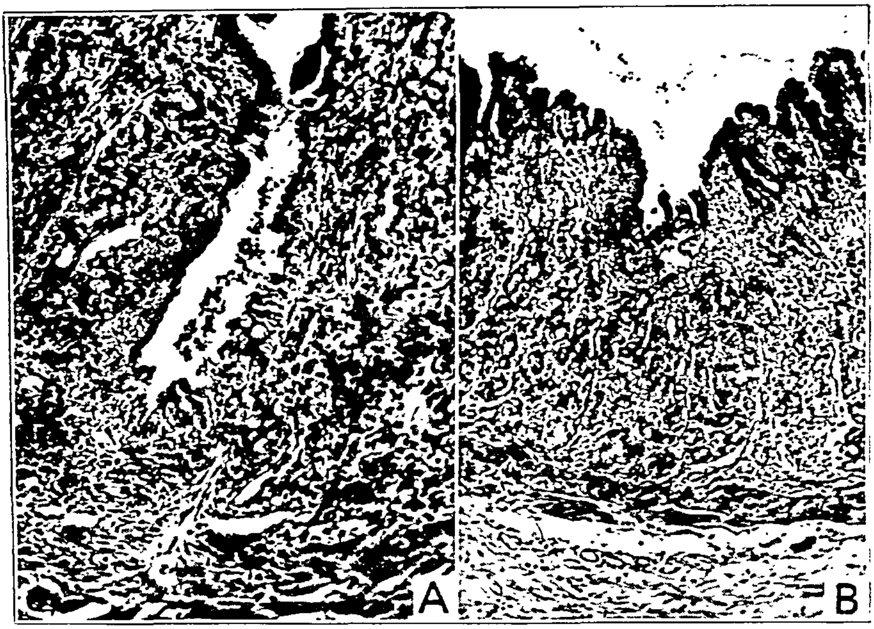

Fig. 3.—*A*, a photomicrograph of the earliest microscopic lesion, showing necrotic mucosal cells sloughing into the lumen of a crypt; × 120. *B*, a photomicrograph of a slightly more advanced lesion than is shown in *A*, picturing destruction of the mucosal cells with a surrounding inflammatory reaction; × 85.

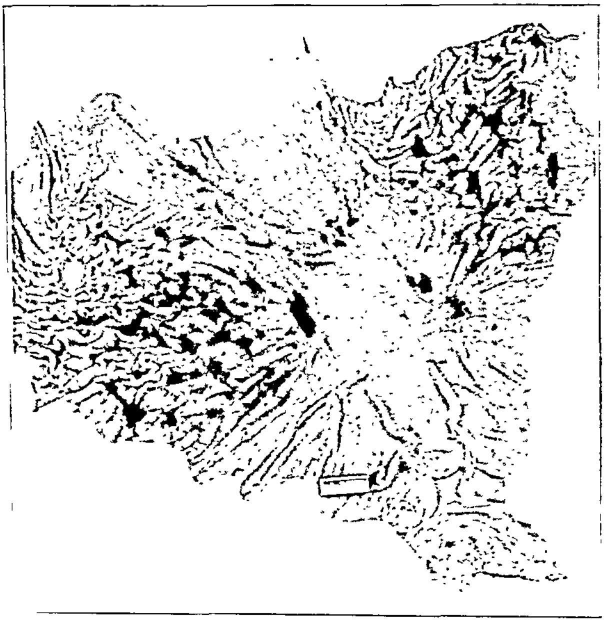

Fig. 4.—A specimen showing multiple acute to subacute gastric ulcers.

usually involved only the mucosa and submucosa but at times involved all layers of the stomach and even perforated.

Microscopically, there was a sharply defined ulceration with a zone of neutrophilic infiltration in the floor of an ulcer (fig. 5). This frequently extended for a considerable distance below the necrotic layer, but for the most part the surrounding tissue had a healthy appearance. There was some edema, especially of the submucosa. The vessels were congested but showed no endothelial thickening. The muscle layer was frequently infiltrated with polymorphonuclear neutrophils.

The Late Ulcer: The multiple acute ulcers healed rapidly, and the diffuse gastritis disappeared. There persisted in the "ulcer-bearing" area a large chronic ulcer situated from 2 to 3 cm. from the pyloric ring on the lesser curvature and posterior wall of the stomach (fig. 6). Occasionally several acute to subacute ulcers were associated with this chronic ulcer, but there was never more than one chronic ulcer in a single specimen.

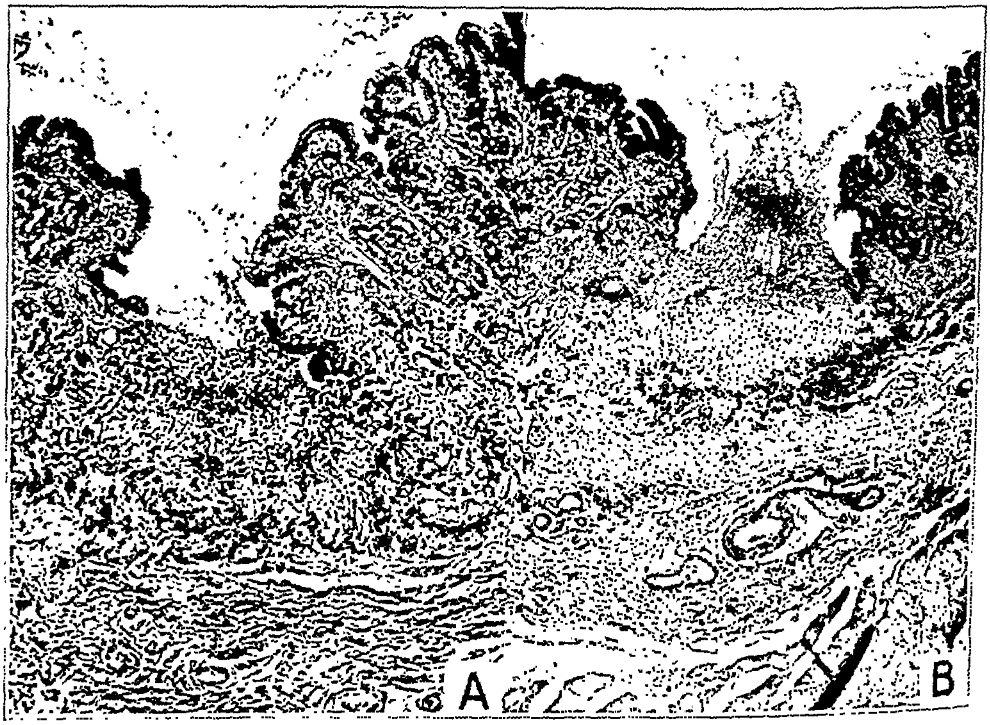

Fig. 5.—*A*, photomicrograph of an acute gastric ulcer with beginning involvement of the muscularis mucosa; × 60; *B*, a photomicrograph of an acute gastric ulcer with involvement of the muscularis mucosa and beginning infiltration of the submucosa; × 30.

The chronic ulcer had an old appearance; it was thick, indurated and rounded and had overhanging edges. There was a dirty, necrotic or granulating floor. At times this floor was formed by the adjacent tissue, namely, the pancreas or liver. Occasionally there was a visible perforation through the base of the ulcer. This was associated with either a localized abscess or a general peritonitis.

Microscopically, there was a superficial zone of molecular necrosis (fig. 7) which rested on vascular granulation tissue. This granulation tissue was markedly infiltrated with fibrous connective tissue and lymphocytes. The muscle layer

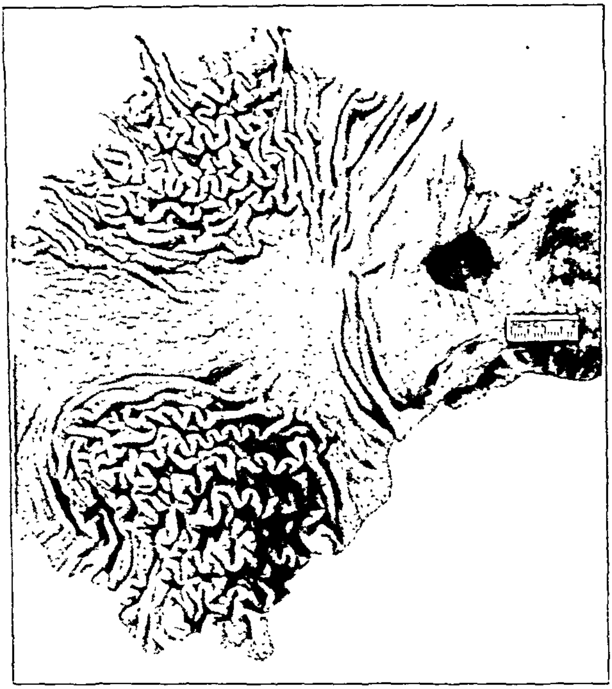

Fig. 6.—A specimen showing a chronic perforated gastric ulcer on the lesser curvature of the stomach with multiple contact ulcers. Thirty-four grams of cinchophen was given in nineteen days.

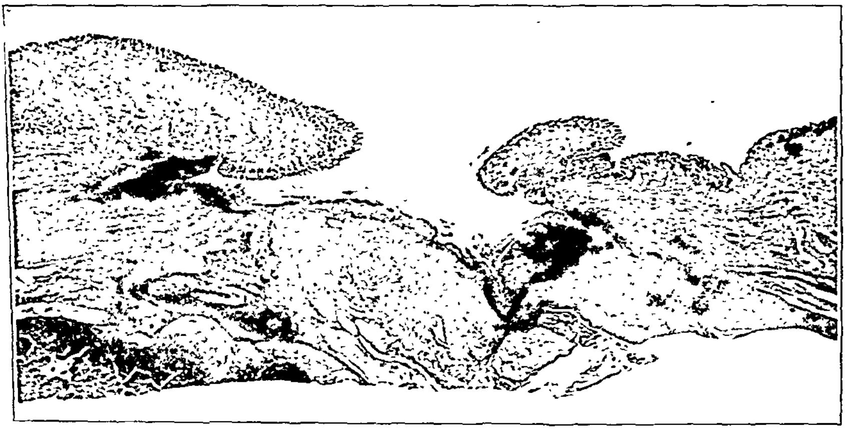

Fig. 7.—A photomicrograph of a chronic perforated ulcer of the lesser curvature of the stomach showing the undermined and rolled over edges, a superficial necrotic layer on a fibrous granulation tissue base and involvement of the omental fat and pancreas in the base; × 3⅞.

was always penetrated and infiltrated with lymphocytes. In many cases the muscle had been replaced by the infiltrated pancreas or fibrous pads of gastrohepatic omentum.

The entire process extended for a short distance laterally. The blood vessels showed endarteritic and endophlebitic thickening with a large number of newly formed vessels. The general shape of the ulcer was variable but was usually funnel shaped or cone shaped.

At the margins of the ulcer there was evidence of proliferative activity on the part of the mucosal epithelium. The slough was lifted a bit or partially removed, and new mucosal cells were seen forming on a clean granulation tissue.

Healing Process: There was a constant attempt at healing in the peptic ulcer produced by cinchophen. When the administration of cinchophen was discontinued, healing of the ulcer rapidly took place. This process was so rapid that no significant difference could be noted when the regular, the kennel or the bone diet was given. The time required for complete healing of the chronic ulcer was from three to five weeks. Complete healing was noted as early as two weeks, but some ulcers required more than seven weeks to heal. Occasionally the ulcer healed while the animal was receiving cinchophen. This was noted only in the dogs which received 1 Gm. of the drug five days a week. It was never noted in the dogs which received 2 Gm. of cinchophen daily.

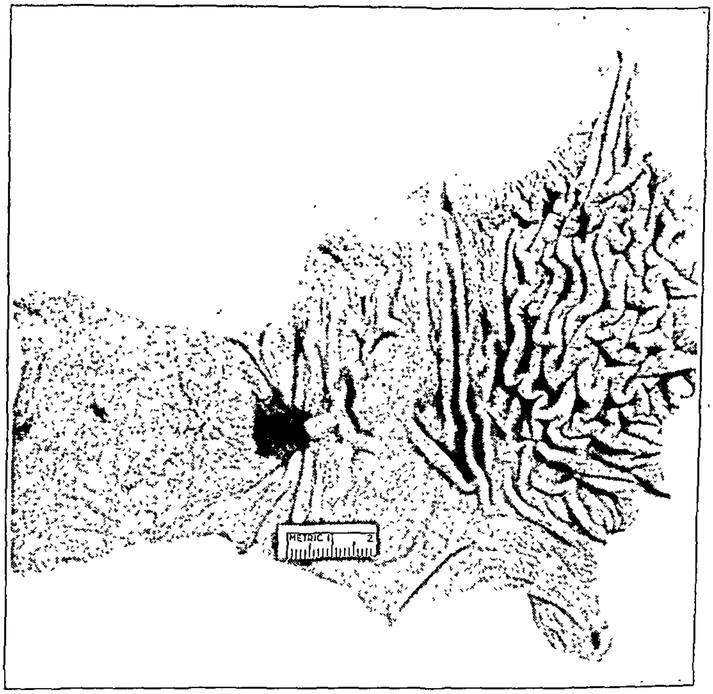

Fig. 8.—A specimen showing a chronic perforated ulcer of the lesser curvature of the stomach after two weeks' healing. The crater is nearly filled with clean granulation tissue; a fibrinous blood clot is seen in the center.

Three days after the administration of cinchophen was discontinued the ulcer had a much cleaner appearance than before. The superficial necrotic layer had disappeared. The clean base was covered by a thin fibrinous blood clot. This clot disappeared at the end of one week after administration of the drug was discontinued. The crater was being filled with vascular, friable, granulating tissue (fig. 8). By the tenth or twelfth day the granulation tissue had a polyp-like appearance and more than filled the crater. The mucosa could be seen growing over the granulation tissue from the edges of the ulcer.

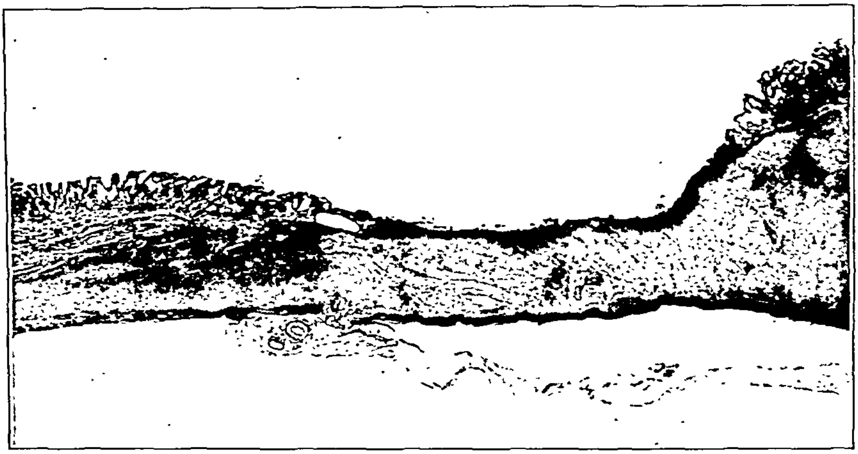

Fig. 9.—A photomicrograph of a chronic gastric ulcer after healing for one week; × 6. One may note the clean granulation layer with the marginal epithelization.

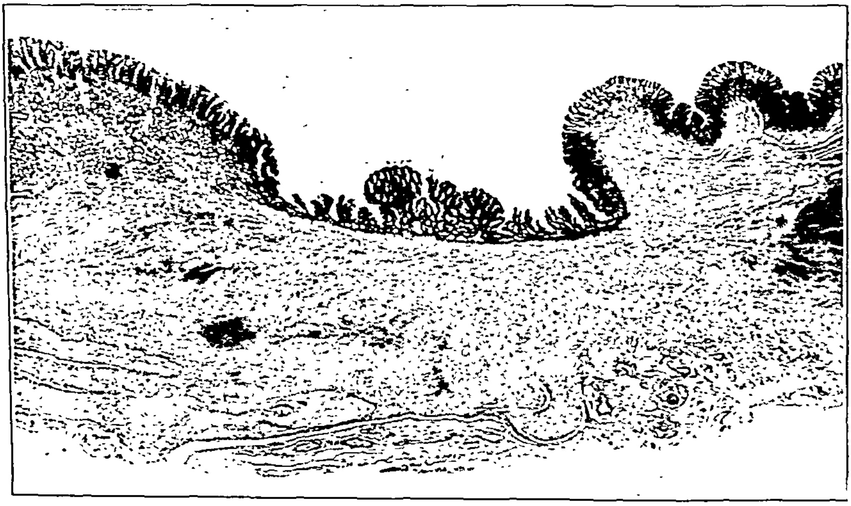

Fig. 10.—A photomicrograph of a chronic gastric ulcer during healing with newly formed mucosa becoming polypoid on a vascular scar tissue base; × 4½.

Microscopic examination revealed the same changes as were seen grossly (fig. 9). In addition, a subsidence of the inflammatory reaction and marked proliferation of the fibrous tissue in the base of the ulcer were noted. The marginal epithelium was seen growing as a single layer of flat or cuboidal cells over the granulating tissue. As this layer of cells progressed, the polyp-like projection of granulation tissue was pinched off. The new mucosal cells rapidly became columnar and were thrown into folds, which in turn formed villi (fig. 10). The mucosal glands then regenerated.

The damaged muscular layer was replaced by fibrosis. This fibrosis extended laterally beyond the defect and in some cases involved the serosa. Many of the blood vessels were obliterated, but many new ones were formed. The completely healed ulcer (fig. 11) was a scar-filled excavation covered by atypical epithelium.

Grossly, this completely healed ulcer (figs. 12 and 13) was recognized early by the raylike arrangement of the surrounding rugae. The regenerated epithelium had a whiter, more roughened and depressed surface than the surrounding mucosa.

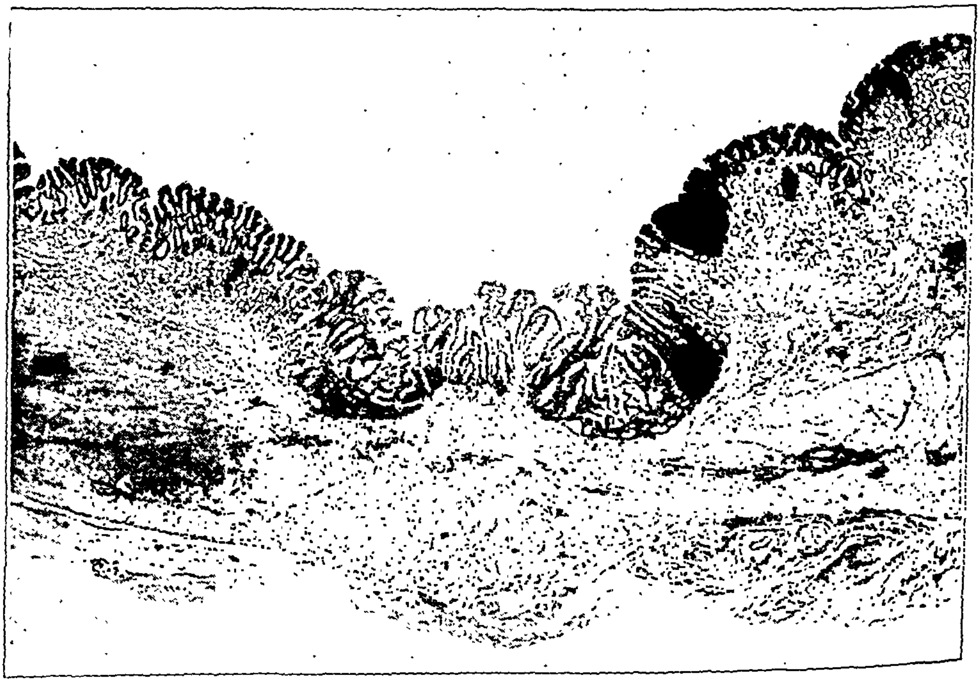

Fig. 11.—A photomicrograph of a completely healed chronic gastric ulcer, showing atypical mucosa on a scar tissue base; × 10.

The healed ulcer was recognized with much greater difficulty at the end of twelve weeks. The mucosa appeared nearly normal, but there remained a persistence of the raylike rugae. Occasionally, the ulcer was recognized by the thickened white fibrous appearance of the serosal surface.

The majority of the dogs which were fed bone had particles of this bone embedded in the fibrotic layer of the healed ulcer. Several active ulcers contained hair, bone and other foreign bodies embedded in the base.

The gross and microscopic pictures of the duodenal ulcer are identical with those of the gastric ulcer.

Comment.—These studies demonstrate that the peptic ulcer produced by cinchophen begins with a destruction of mucosal cells. This occurs throughout the gastric mucosa and is associated with diffuse gastritis. There is hemorrhage from the mucosal blood vessels. The mucosal

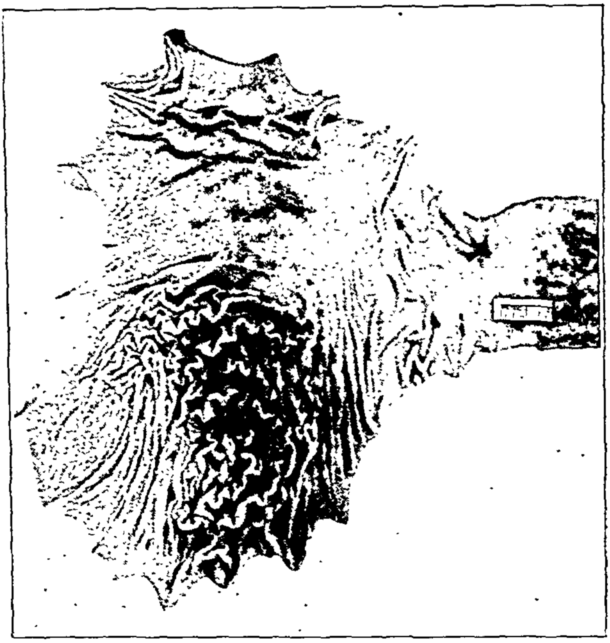

Fig. 12.—A specimen with a chronic perforated ulcer on the posterior wall after six weeks' healing, showing the mucosa rolled from above over a small unhealed crater and spokelike contraction of the mucosal folds.

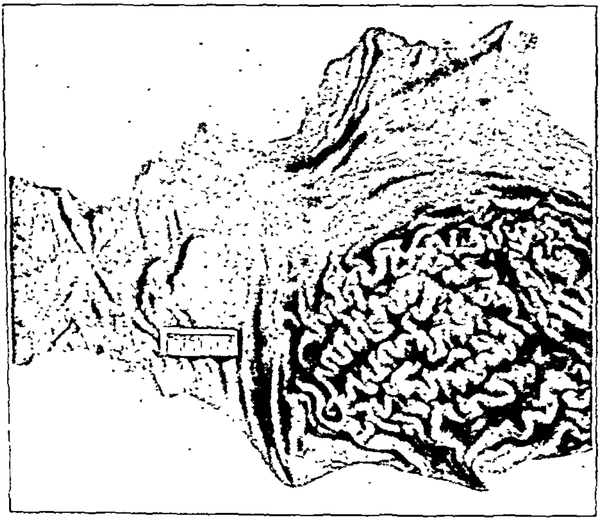

Fig. 13.—A specimen with a completely healed chronic perforated pyloric ulcer of the lesser curvature.

erosions progress as a result of digestion by the gastric contents and become multiple acute ulcerations. These acute ulcers heal, and the gastritis disappears. The acute ulcers in the gastric pathway, probably because of the trauma and increased digestion of tissue, progress and become chronic ulcers.

An ulcer heals rapidly when the administration of the cinchophen is stopped. The fact that the feeding of bone made no apparent difference in the rate of healing is interesting. It was shown that this traumatizing agent contacted the ulcer, because it was found embedded in the base of the ulcer. It cannot be definitely said that this irritant had no effect on the rate of healing, but there was none that could be accurately demonstrated. The etiologic factor was removed when the administration of the drug was stopped.

Pathologically, the peptic ulcer produced by cinchophen was identical in every respect with the peptic ulcer seen in man. The final true ulcer is a chronic lesion. This then gives us a method for consistently producing an experimental chronic peptic ulcer. This could be done consistently heretofore only by surgical means. This process presents itself as an invaluable one, because it opens up to a greater degree the possibility of experimental study of the chronic peptic ulcer.

SUMMARY

The administration of cinchophen is an effective method for the production of chronic peptic ulcer in dogs. Peptic ulcer developed in 95.8 per cent of the animals after the oral administration of cinchophen. A few duodenal ulcers occurred, but the majority of the ulcers were gastric. The use of bone as a mechanical irritant increased the rapidity of the formation of ulcer but did not demonstrably influence the rate of healing. Cinchophen administered by rectum, parenterally, through intestinal fistulas or orally to dogs which had fundic pouches produced peptic ulcer in all instances, which proved that ulcer occurred after absorption of the drug. The ulcer begins with an initial destruction of mucosal cells. The progression and healing are similar to those observed in other experimental peptic ulcer and in ulcer in man.

CEREBRIFORM NEVUS RESEMBLING CUTIS VERTICIS GYRATA

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The condition now known as cutis verticis gyrata was first described by Robert in 1848. The second example of this disease was recorded by Devergie (cited by Meirowsky) in his book "Traité pratique des maladies de la peau," which was published in 1854. In 1893 McDowell, an English neuropsychiatrist, described a similar case occurring in an epileptic microcephalic idiot. In the same year, Cowan reported 2 cases of the same nature, occurring in idiots. Jadassohn, at the Ninth Congress of the Dermatological Society in 1906, in Bern, presented a patient whose scalp in the occipital region was arranged in irregular folds, varying from 0.75 to 1.5 cm. in width. He later reported 2 additional cases. Unna in 1907 reported 3 cases of a similar nature. These cases were characterized by a gyrate appearance of the scalp over the vertex and the back of the head, resembling in appearance the furrows and convolutions of the cerebrum. He called the condition cutis verticis gyrata, and this name is the one most commonly employed today. Von Veress introduced the term "cutis verticis striata" to designate the 11 cases which were reported by him in 1908. In 1909 Audry introduced the name "pachydermie occipitale vorticellée" in describing his case. Stratton in 1933 found 158 cases reported by 87 different authors during a complete review of the literature on the subject.

GENERAL CHARACTERISTICS OF CUTIS VERTICIS GYRATA

Cutis verticis gyrata is a disease of the scalp characterized by the presence of a variable number of convolutions, or gyri, separated by furrows, or sulci. It is usually situated in the posterior parietal and occipital regions, although any portion of the scalp may be involved. The convolutions and furrows may be more or less parallel, running anteroposteriorly, from side to side or diagonally across. Less often they may be irregularly situated. The convolutions are permanent and ineffaceable, so that they can neither be made to disappear by traction on the skin nor be produced by pressure and counterpressure on the scalp. There are, in general, two main variables of this disease.

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In the first type the gyri are less markedly elevated and merge imperceptibly into the adjacent normal scalp, a definite line of demarcation between the abnormal and the normal being absent. The maximum change is generally in the midline and extends symmetrically in all directions, becoming less and less marked as the periphery is approached.

The second type is characterized by a definite circumscribed tumor with raised abrupt borders. The convolutions in this type are more prominent and the furrows deeper, closely simulating the appearance of the cerebrum. The growth does not tend to be symmetrically situated. Another distinguishing feature is that it occurs more frequently in females and is usually present from birth. This type is caused by a nevus, usually of the pigmented variety. Slow growth is the rule, although periods of more rapid growth are not uncommon. Whereas the first type is usually inconspicuous and discovered accidentally, the second type forms a prominent tumor mass which is obvious to the patient for a long time.

ETIOLOGY AND CLASSIFICATION OF CUTIS VERTICIS GYRATA

For many years considerable confusion and disagreement existed in the minds of various authors concerning the exact etiology of cutis verticis gyrata. This was largely due to the fact that it was not generally recognized that this disease may be related to several different etiologic factors.

In 1893 McDowell suggested that the cutaneous folds were due to hypertrophic muscles of the scalp, similar to the folds noticed when a dog "pricked his ears." It seems reasonable to assume that in some cases cutis verticis gyrata represents a reversion to a period when the muscles of the scalp could move the scalp at will. Fischer (1922) expressed the belief that the anomaly in certain cases is developmental and is comparable to the conditions present in the scalps of many mammals, such as lions, tigers and bulldogs. The occurrence of cutis verticis gyrata in idiots tends to support these views.

Jadassohn in 1906 and Unna in 1907 regarded the condition as the result of an anomaly of development and classified their cases as belonging to the larger general group of nevi. This view was supported by Silvestri (1909) and Rouvière (1911). Malartic and Opin (1914) and Lenormant (1920) definitely established the nevic nature in their cases by histopathologic examination. Various inflammatory diseases of the scalp were considered as the etiologic agents by von Veress in 1908 and by Audry in 1909. In 1911 Sabat reported a case associated with acromegaly, and Adrian (1916) and Grönberg (1927) suggested a causal relationship between the two diseases. Galant (1918) and Stühmer (1922) expressed the belief that the condition in their cases had developed on a traumatic basis.

Von Veress (1908), Pospĭeloff (1909) and Wise and Levin (1918) found cutis verticis gyrata associated with syphilis. It was not demonstrated by any of these observers that an actual syphilitic infiltration of the scalp was responsible for the abnormality, although a generalized syphilitic infection was present at the time the patients were first examined. Fischer in 1922 advanced the theory that in some cases the condition could be explained on the basis of an anomalous and apparently congenital hypertrophy of the connective tissue of the scalp. Oliver in 1922 offered the explanation that in time a chronic inflammatory process in the scalp produces fibrous tissue, which by contracting gives rise to furrowing of the scalp. Pelagatti (1924) described a case in which the anomaly was due to a leukemic infiltration of the scalp. Truffi (1930) reported a case in which pemphigus seemed the causative factor.

In 1933 Stratton argued that the anatomic construction of the scalp might explain the condition, since so many unassociated causes apparently resulted in the same deformity. He stated that in the scalp strong fibrous bands run diagonally and perpendicularly through the fat, firmly connecting the galea aponeurotica and the skin. It was conjectured that the fat was replaced by the infiltrating cells but that the fibrous bands were not. This resulted in gyri and sulci, or the formation of cutis verticis gyrata. He thought that the size of the gyri depended directly on the intensity of the infiltration.

Fischer (1922) greatly simplified the entire subject of cutis verticis gyrata by offering an etiologic classification which served to correlate the many conflicting views regarding etiology. His classification is as follows:

A. True cutis verticis gyrata—a developmental anomaly representing a reversion to a lower form of life when the muscles of the scalp could move it at will.

B. Diseases of the scalp "in the form of" cutis verticis gyrata.

1. Inflammatory changes, acute and chronic, e. g., eczema, psoriasis, folliculitis and impetigo.
2. Anomalous and apparently congenital hypertrophies of the connective tissue.
3. Tumors, such as nevi and neurofibromas.
4. Changes in the scalp occasioned by diseases that lead to proliferation of the tissues, such as acromegaly, myxedema, leukemia and cretinism.

To this classification might be added:

5. Changes in the scalp resulting from trauma.

In the present study, reports of 117 cases of cutis verticis gyrata were found in the literature. We have attempted to group these cases according to Fischer's classification. There were 9 cases of true cutis verticis gyrata, forming 8 per cent of the total. Eighty-five cases of diseases of the scalp "in the form of" cutis verticis gyrata were found, aggregating 72 per cent of the entire number. In 22 cases, or 19 per cent, the data given were insufficient to permit an accurate classification.

Of the 85 cases which fell into the second group, 26 (22 per cent) were caused by inflammatory changes; 4 (3 per cent) resulted from anomalous and apparently congenital hypertrophy of the connective tissue; 24 (21 per cent) were due to neoplasms, all of which were nevi; 26 (22 per cent) were occasioned by diseases that lead to proliferation of the tissues, and 6 (5 per cent) were consequent on trauma.

The 26 cases occasioned by diseases that lead to proliferation of the tissues have been further subdivided into 19 cases associated with acromegaly, 1 case caused by a leukemic infiltration of the scalp, 4 cases apparently due to syphilis and 2 cases in cretins.

HISTOLOGIC PICTURE OF CUTIS VERTICIS GYRATA

Naturally, the histopathologic picture of the disease will vary according to the etiologic agent.

We have found no observations on the histopathologic picture in cases of true cutis verticis gyrata or in cases of changes in the scalp in the form of cutis verticis gyrata resulting from trauma. Neither have we noted any observations concerning the histopathologic picture in cutis verticis gyrata occasioned by diseases that lead to proliferation of the tissues.

Von Veress (1908), Vignolo-Lutati (1910) and Hannay (1923) have reported their microscopic observations in cases of cutis verticis gyrata following inflammatory diseases of the scalp and, in general, their descriptions are in agreement. According to them, the epidermis exhibited no change. In the deeper parts, infiltrations of plasma, lymph and mononuclear cells could be seen, often localized about the deeper follicles. Von Veress reported a complete disappearance of elastic fibers. Atrophy of the sebaceous and sweat glands occurred in some cases, while von Veress found a disappearance of the sebaceous glands in his cases. No excessive pigment formation was seen.

The histopathologic picture in the group of cases caused by an anomalous and apparently congenital hypertrophy of the connective tissue is self-explanatory. Ota (1931) found hyperplasia of the sebaceous glands with a thickening of the connective tissue of the cutis.

Tumors in the form of cutis verticis gyrata have been described by various authors. Malartic and Opin (1914) and Lenormant (1920) saw large numbers of nevus cells beneath the epidermis as the characteristic feature in their cases. Alderson (1927) found dense collections of pigment in the upper layer of the corium and large whorls or cords of connective tissue in the lower layer. No nervous tissue was seen. Grieve and Biddle (1931) noted pigmented nevoid cells just beneath the epidermis. In their cases the connective tissue was very cellular and vascular and was arranged in concentric bundles or whorls, especially well marked in the deeper layers of the corium. Madden (1935) reported an unusual case of cutis verticis gyrata due to a melanoma which had undergone malignant degeneration.

ORIGIN AND NATURE OF THE NEVUS

For many years there has been a divergence of opinion as to the origin of the nevus. There are, in the main, two schools of thought on the subject. One considers the nevus to be of mesodermal origin, and the other, of ectodermal origin. Each theory has been strongly supported by recognized investigators.

It is of interest to review a more recent conception of the origin of the nevus because this view seems entirely plausible and is being more and more widely accepted today.

Soldan in 1899 observed the association of nevus cells with sensory nerve elements and advanced the opinion that the nevus, like a neurofibroma, was formed by proliferation of the connective tissue of the sensory nerves of the skin. The pigmentation was considered to be a consequence of this fibromatosis.

Recently, by special staining methods, Masson (1926, 1931, 1932 and 1933) presented convincing evidence to show that the nevus and the melanoma are formed not by an abnormal proliferation of the connective tissue of the nerve sheaths but by a proliferation of the ends of the cutaneous sensory nerves. He expressed the belief that in the dermis the nevus cells arise from the cells of Meissner's corpuscles; that in the epidermis they come from the specialized tactile corpuscles of Merkel-Ranvier, and that they originate from the special pigment cells known as chromatophores in both situations. He has observed many features of nevus formation in the pigmented spots in the skin in Recklinghausen's disease and has found miniature neurofibromas in connection with nevi. He, therefore, accepts the relation of the nevus to neurofibromatosis. It is Masson's opinion that all nevi are neuronevi and that all are neuromatous terminations of tactile nerves. This theory serves to harmonize the ectodermal and mesodermal theories of origin and is supported by Ewing (1928), Stout (1932), Foot (1932), Weller 1936) and many others.

TREATMENT OF CUTIS VERTICIS GYRATA

The treatment of this disease has depended greatly on the etiology and nature of the abnormality. No treatment has been advocated for those cases not caused by a nevus, except for the treatment of the underlying disorders such as inflammatory diseases, myxedema, acromegaly, etc. The literature contains no report of a cure of cutis verticis gyrata of this type after improvement or cure of the causative factor. As a rule, surgical treatment is not indicated, because, first, there is little demarcation between the normal and the abnormal scalp, so gradually does the one blend into the other; and, secondly, the patient does not desire radical treatment for a lesion causing so little inconvenience and deformity.

However, in those cases in which the condition is caused by a nevus, one is dealing with a circumscribed, deforming tumor which has malignant potentialities. As for a nevus elsewhere, the treatment is surgical. There are two types of procedure: (1) complete excision with subsequent skin grafting, if a primary closure cannot be effected, or (2) gradual partial excision with closure. The latter method was advocated by Davis in 1934 in the operative treatment of hemangioma.

Davis stated that this method is of value when the growth cannot be entirely removed at one operation with immediate primary closure, either because the defect is too large or because it is in a situation where there is insufficient lax tissue to allow an immediate closure. We have found it a worth-while method in treating a large nevus of the scalp. In this procedure an elliptic incision is made in the tumor, and as much of the growth as possible is removed, but not enough to interfere with immediate closure of the wound. According to Davis, after healing is complete, in order to allow stretching of the surrounding tissues, at least two months should elapse before the second operation. This is carried out in exactly the same manner, and the procedure is continued with similar intervals until the growth is completely eradicated. During the intervals massage is helpful in stretching the skin. The objection may be raised that the trauma caused by partial excision might possibly result in malignant degeneration. It is an alternative method that may be used in certain cases in which the condition does not lend itself to complete excision with subsequent primary closure or skin grafting.

In this discussion it is of interest to note the differences of opinion among different writers as to the most satisfactory form of treatment of a nevus. These methods of therapy range from the application of the electric needle, solid carbon dioxide, cautery, caustics, radium and liquid air to electrolysis, roentgen irradiation, endothermy, electrodesiccation and electrocauterization. We believe that the best form of treatment is complete surgical excision.

REPORT OF CASES

Two cases of cerebriform nevus of the scalp resembling cutis verticis gyrata have recently been observed at the University Hospital.

Case 1.—H. K., a 9 year old white American school girl, was admitted to the clinic on July 25, 1933, complaining of a growth on the side of the head. This lesion had been present since birth and had been increasing in size recently. It caused her no discomfort, but the parents desired its removal for cosmetic reasons. There was no history of any other disease of the scalp or of injury to the scalp. The patient had no other complaints.

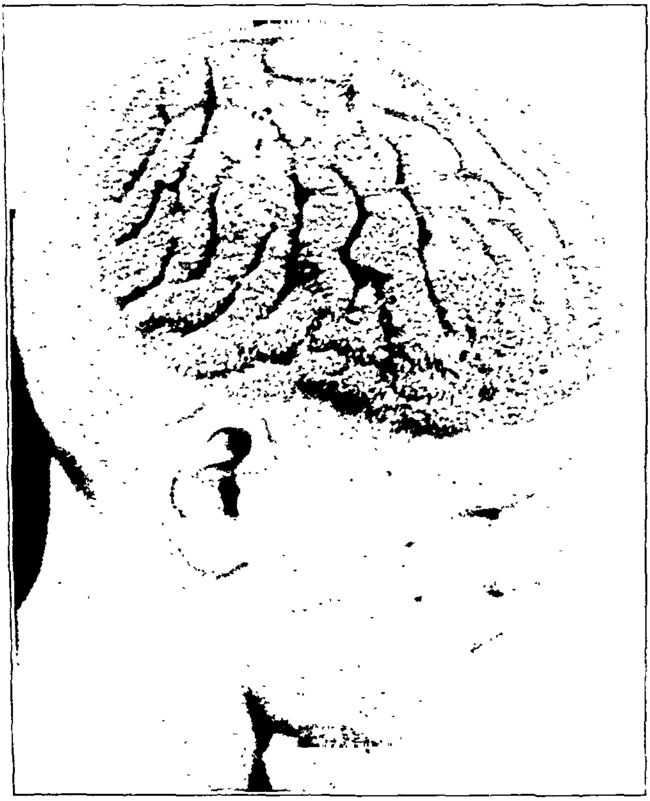

Fig. 1 (case 1).—Cerebriform nevus of the scalp resembling cutis verticis gyrata.

Her past history was essentially irrelevant. There was no history of a similar deformity in either parent and no history of syphilis.

Physical examination revealed a healthy, well developed, well nourished girl of normal mentality. A circumscribed tumescence covered with hair presented itself on the right parietofrontal region of the scalp. It was approximately 15 cm. long and 12 cm. wide and extended from the vertex to within 1 inch (2.5 cm.) of the right ear and from the occipital region posteriorly to the hair line of the forehead anteriorly. This tumor was composed of multiple gyri separated by rather deep furrows and was distinctly demarcated from the surrounding scalp by its raised abrupt edges. The gyri were rather soft and closely resembled cerebral convolutions. One portion of the growth exhibited a violaceous color. The tumor was not attached to the underlying bone. There was no evidence of inflammatory disease of the scalp. Whitish particles the size of a pinhead were attached firmly to the hair (figs. 1 and 2).

The remainder of the physical examination revealed nothing significant.

The results of the laboratory examinations were negative. The hemoglobin content was estimated to be 80 per cent (Sahli) ; the leukocytes numbered 6,400 per cubic millimeter. The urine was normal, and the Kahn reaction of the blood was negative. Roentgen examination of the skull revealed no bony abnormality.

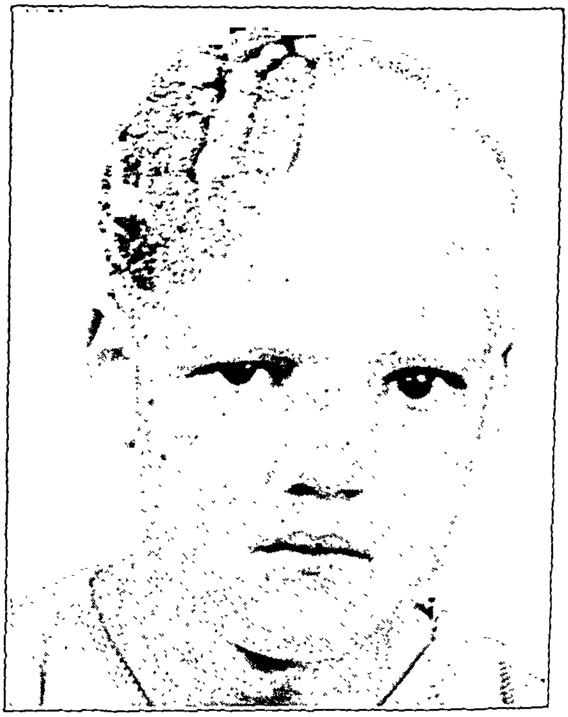

Fig. 2 (case 1).—The nevus as seen from the front.

Diagnoses of pigmented nevus of the scalp and pediculosis capitis were made, and surgical excision was advised.

Accordingly, on August 10, with the patient under anesthesia with tribromethanol in amylene hydrate and nitrous oxide curved vertical incisions were made through the central portions so as to excise an ellipse of the tumor. The tumor tissue showed no unusual vascularity. The edges of the tumor were then mobilized and sutured together with black silk, obliterating the operative defect. The tumor tissue removed measured 15 by 6.5 cm. Convalescence was uneventful. The wound healed by primary intention, and the patient was discharged on September 2.

She was readmitted to the hospital on November 11. The history for the interval between discharge and admission was unimportant. Examination revealed no change in the character of the tumor except for the diminution in size, resulting from the first partial excision. On November 11, with the patient anesthetized with tribromethanol in amylene hydrate and nitrous oxide, an elliptic sagittal incision was made through the temporal part of the mass, extending down to the pericranium. The ellipse of tumor was then removed. The edges of the skin were approximated without undue tension and sutured with interrupted black silk. This portion of the tumor measured 15 by 3 cm. The postoperative course was without event, and the patient was discharged on December 1.

She returned on June 12, 1934, giving an unimportant history for the interval between discharge and admission. Examination gave negative results, except for the presence of the remaining portion of the tumor. On June 16, the same type of anesthesia being used as before, a narrow elliptic incision was made in the sagittal direction of the scalp, and the remaining portion of the tumor was excised. The edges of the skin were mobilized and closed without undue tension with black silk. This portion of the tumor measured 15 by 3 cm. The convalescence was entirely satisfactory, and the patient left the hospital on June 27.

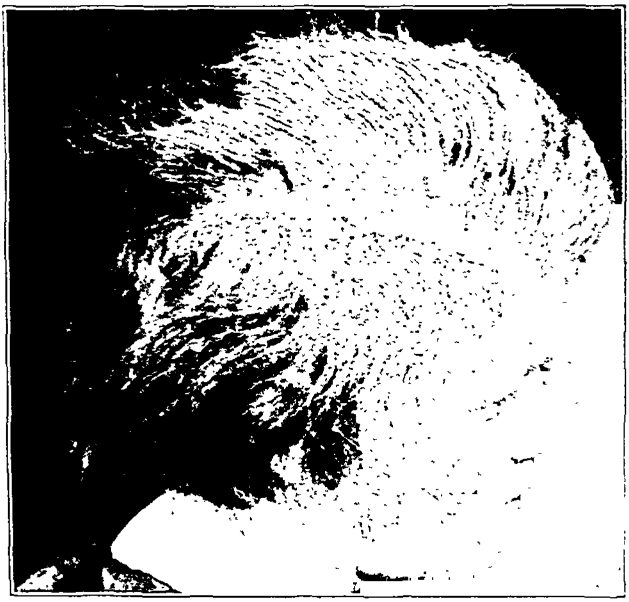

Fig. 3 (case 1).—The operative scar and areas of hyperpigmentation in the surrounding skin. These cannot be seen when the hair is dressed naturally.

A check-up examination on August 22 revealed an excellent result.

The patient was last seen on March 20, 1935 (fig. 3). There was no indication of recurrence, and the result was satisfactory. The scalp in the region of the operative scar revealed areas of hyperpigmentation, which disappeared at the hair line and were not visible when the hair was normally dressed.

The histopathologic description of the excised tissue was as follows (Dr. C. V. Weller): "The highly convoluted scalp is covered by an atrophic squamous epithelium beneath which there are many nests of typical nevus cells, producing large amounts of melanin. In the deeper portions, the proliferation assumes a pronounced fibroblastic character with a whorling architecture, so that, in many fields, the appearances are those of a typical neurofibroma with all the intervening nevoid gradations being demonstrable. In the neurofibromatous portion, no melanin production occurs. This is a pigmented nevus, showing very beautifully the combination of neurofibromatous areas and medullary nests of nevus cells" (fig. 4).

Case 2.—M. L., a 22 year old white American woman, was admitted to the University Hospital on May 29, 1934, complaining of a tumor on the back of her head and swollen glands in the neck. The growth had been present since infancy and had slowly increased in size. Two months before entrance to the hospital the growth had become painful, and she had noted chills and fever. She thought that one portion of the tumor had become infected and had "drained" for a short time. At that time the glands of the right side of the neck had become tender and swollen and had remained in that condition. Her history was otherwise noncontributory. There was no history of syphilis, inflammatory disease of the scalp or trauma to the scalp. The patient had been overweight for many years.

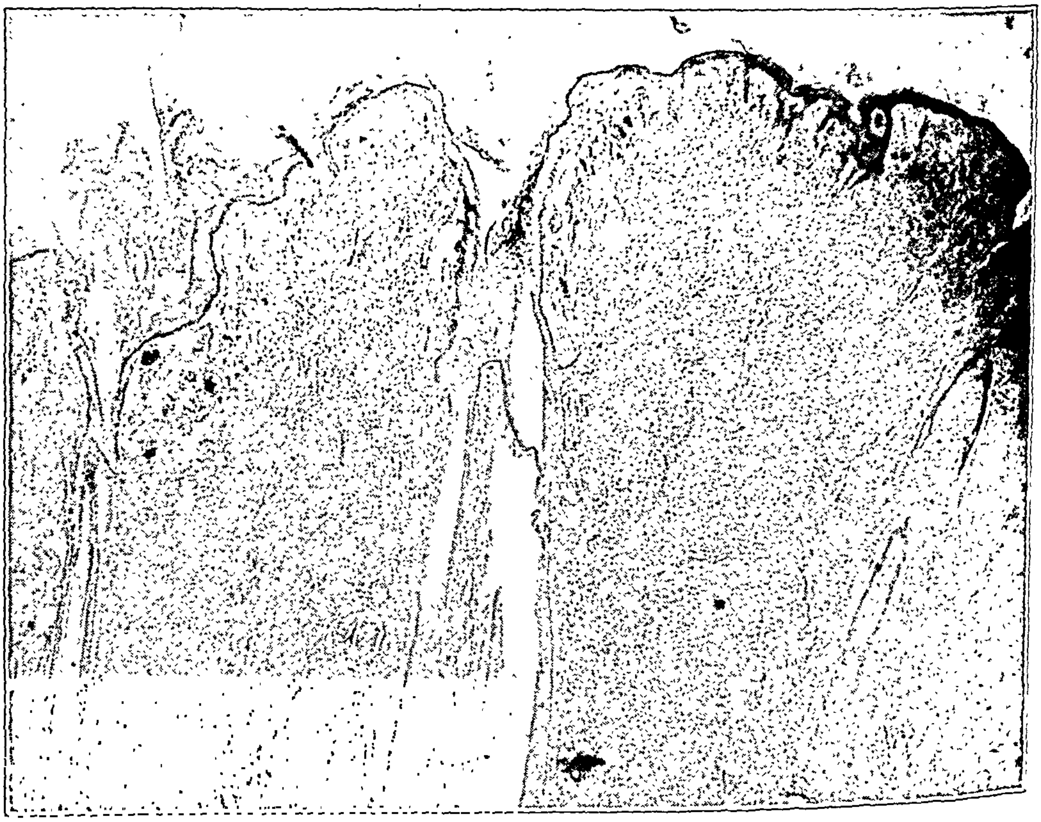

Fig. 4 (case 1).—Superficial medullary nests of nevus cells producing melanin and more deeply situated neurofibromatous areas (× 24).

Physical examination revealed a very obese white woman, appearing the stated age of 22 and having a normal mentality. There was an unusual tumor situated in the posterior portion of the scalp. It was an elevated, circumscribed growth, roughly circular in outline, extending from the vertex to the lower occipital region, posteriorly and to within 1 inch of either ear laterally. It was orange-red and measured 25 cm. in its greatest vertical diameter and 20 cm. in its greatest horizontal diameter. The surface was elevated 2 cm. above the surrounding scalp.

It presented many rubbery, firm nontender nodules and convolutions separated by furrows which, in part, greatly resembled convolutions of the cerebrum. The hair was rather thick in the sulci and sparse over the surface of the convolutions. The tumor was movable over the underlying skull. No inflammation was present. The cervical lymph nodes in the right anterior and posterior triangles were slightly enlarged and tender (fig. 5). The remainder of the physical examination revealed nothing significant. The examinations of the blood and urine gave essentially negative results. The Kahn test of the blood was negative.

Diagnoses of nevus of the scalp and obesity were made.

Due to the depth and firmness of the convolutions in various parts of the tumor, complete excision with subsequent skin grafting seemed to be the procedure of choice. Therefore, on June 4, the patient being anesthetized with tribromethanol in amylene hydrate and nitrous oxide, a circular incision was made about the periphery of the tumor, which was then elevated. A definite line of cleavage was found in the subaponeurotic space, and the tumor was thus easily removed. The edges of the skin were sutured to the pericranium to prevent retraction. Bismuth tribromphenate was used in dressing the wound (fig. 6). The convalescence was uneventful. On June 23, with the patient under nitrous oxide anesthesia, split thickness skin grafts were taken from the posterior aspect of the right thigh and applied to the denuded area on the posterior aspect of the scalp by suturing them to each other and to the surrounding skin. A sea-sponge pressure dressing was applied. The grafts were successful (fig. 7). The donor areas on the thigh were epithelialized completely in about twelve days. The patient was discharged from the hospital on July 28.

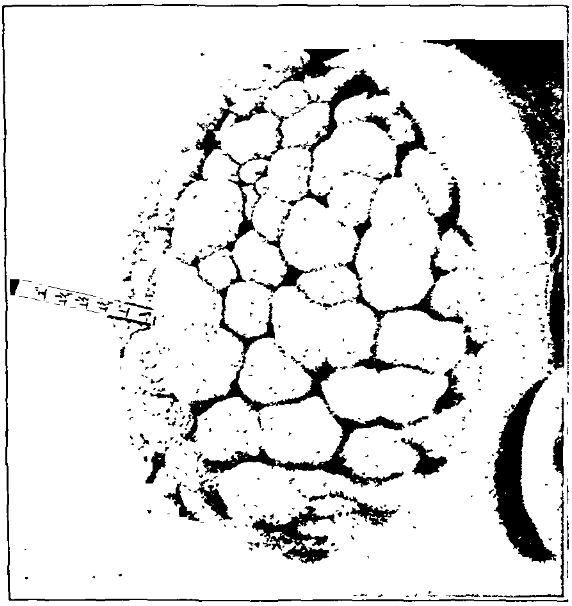

Fig. 5 (case 2).—Cerebriform nevus of the scalp resembling cutis verticis gyrata.

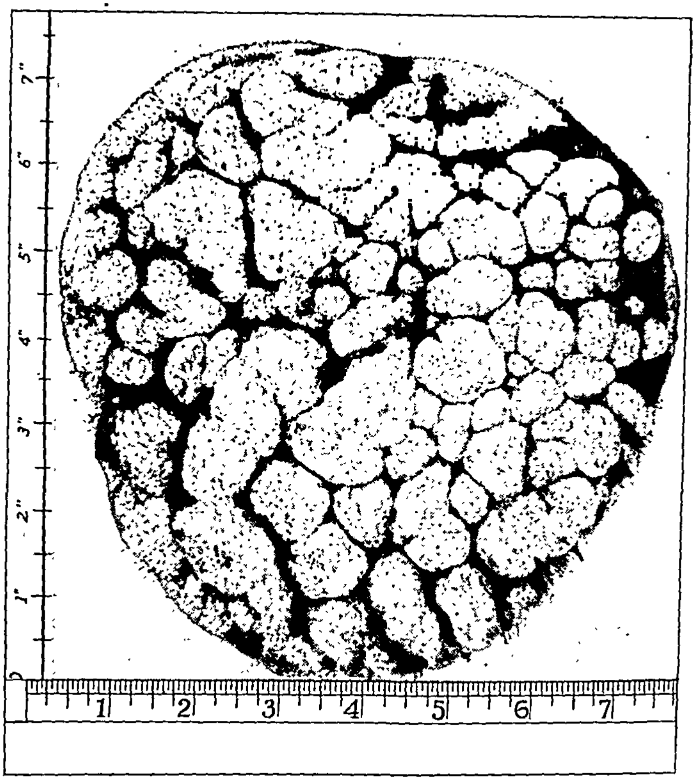

Fig. 6 (case 2).—Appearance of the nevus after its removal.

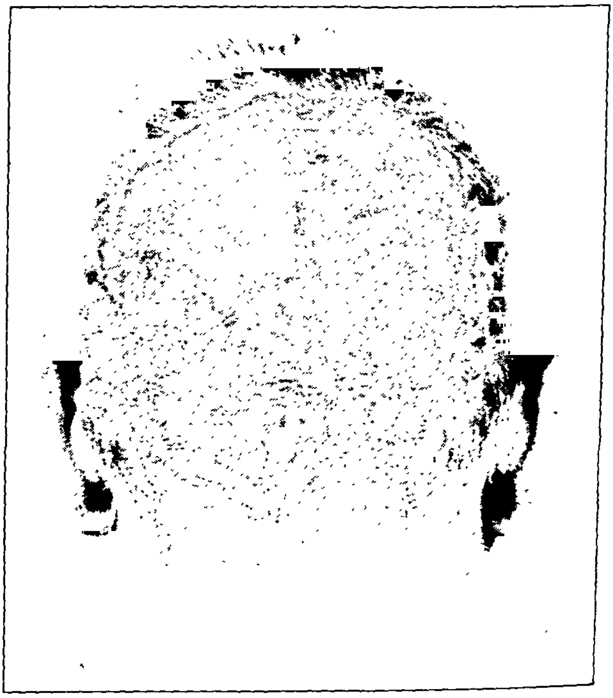

Fig. 7 (case 2).—The operative defect covered by skin grafts.

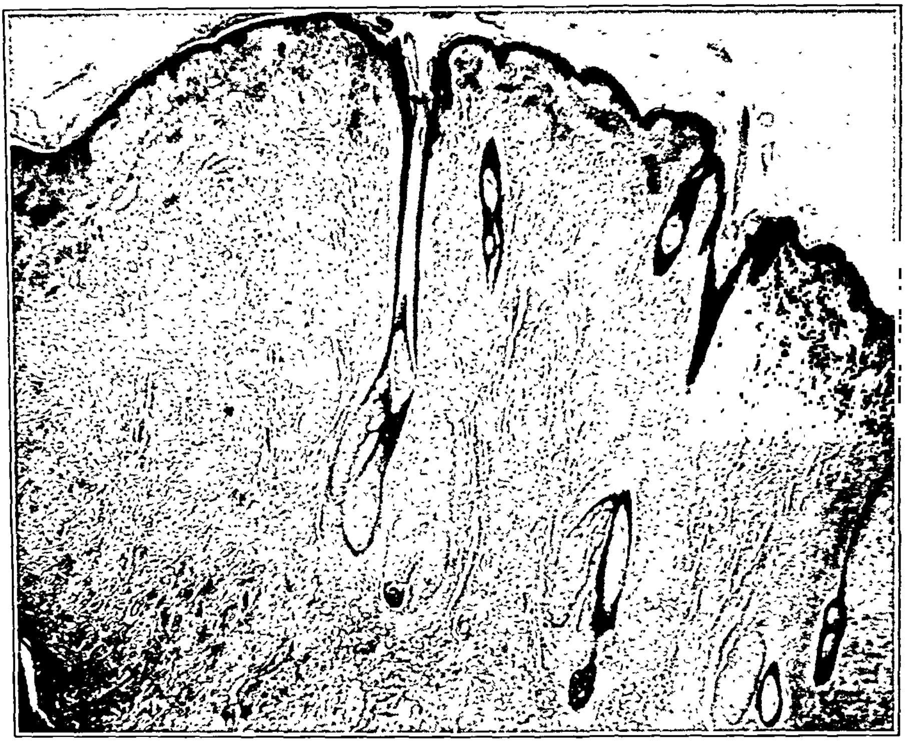

Fig. 8 (case 2).—Photomicrograph of the nevus (× 24).

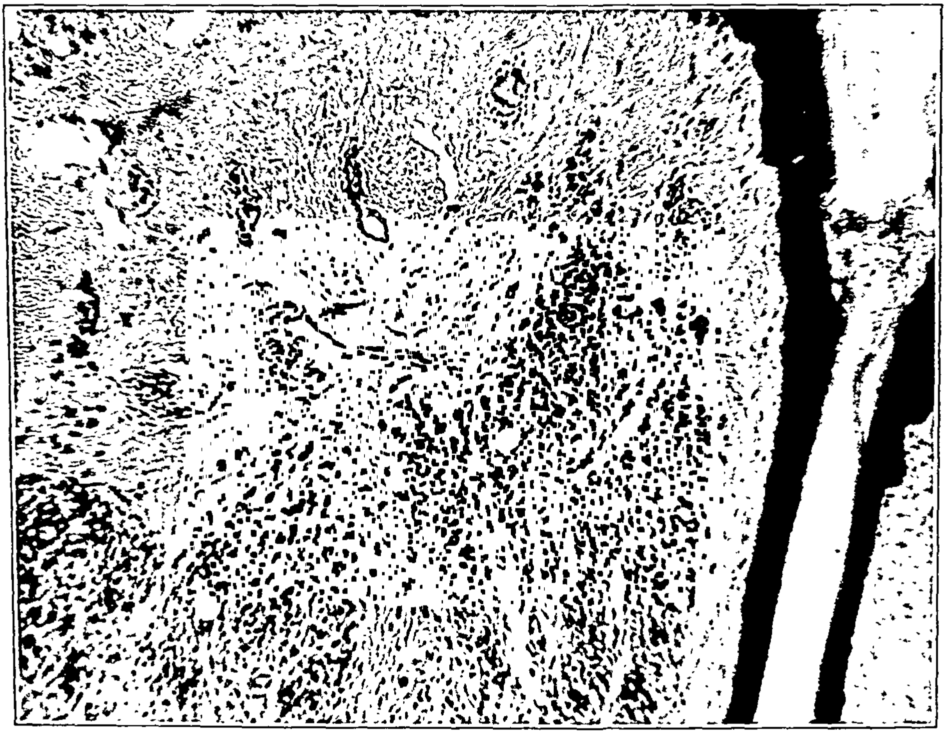

Fig. 9 (case 2).—Photomicrograph showing the nevus cells close beneath the epithelium (× 110).

On March 15, 1935, she reported by letter that she was well and that there had been no sign of recurrence.

The histopathologic description of the neoplastic tissue was as follows (Dr. C. V. Weller): "The scalp is thrown into convolutions by a marked thickening of the corium. There is a widespread proliferation of nevus cells, many of which grow in small nests and cords close beneath the papillomatous squamous epithelium. In the deeper portions, the proliferation assumes a markedly fibroblastic character, whorls of stroma containing elongated cells with spindle-shaped and ovoid nuclei being prominent. In these regions, the appearances suggest those of a neurofibroma" (figs. 8, 9 and 10).

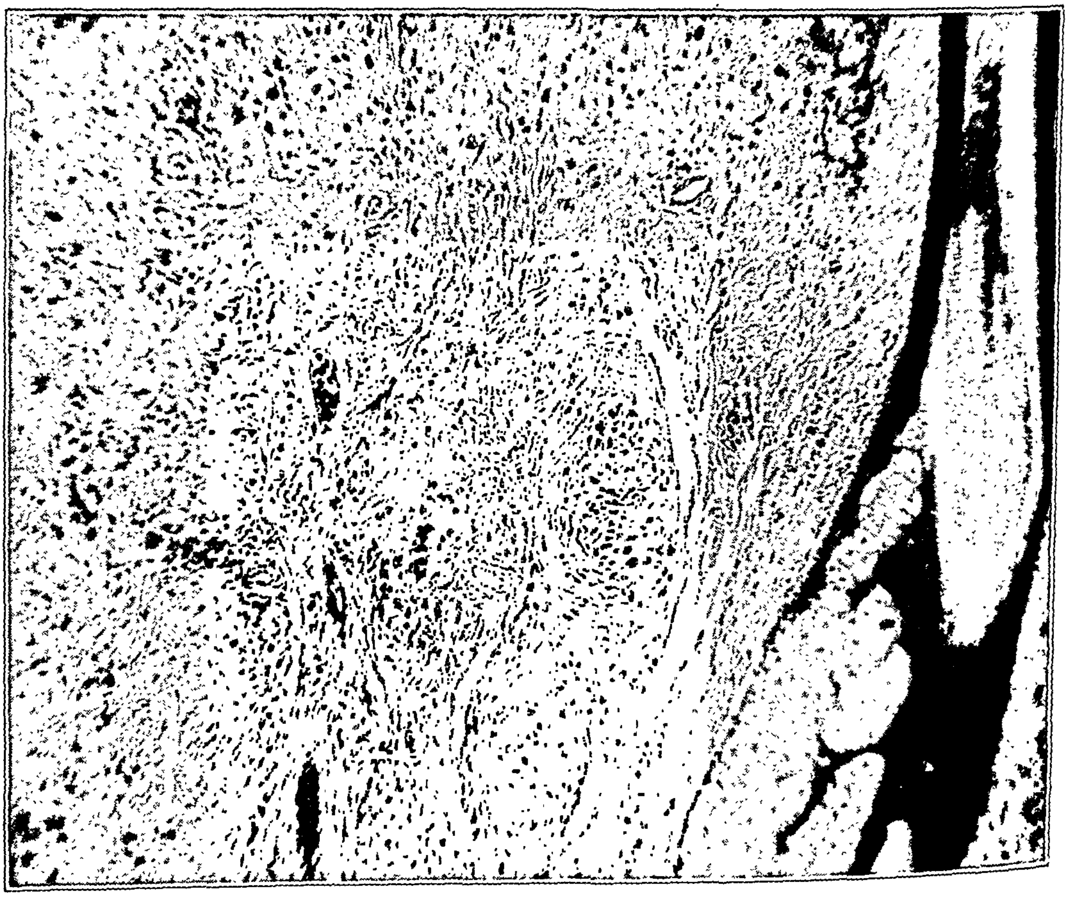

Fig. 10 (case 2).—Photomicrograph of a deeper portion showing the neurofibromatous areas (× 110).

COMMENT

As already indicated, the particular nevus of the scalp reported here constitutes a condition distinctly different, both clinically and pathologically, from all the other types of cutis verticis gyrata. Since this condition presents so few features in common with cutis verticis gyrata, we suggest that it be removed from this classification and designated as cerebriform nevi of the scalp. An interesting commentary in this connection is the fact that in the literature and textbooks this convoluted nevus is referred to as cutis verticis gyrata when it occurs on the scalp.

but as nevus cerebriformis or cerebelliformis when it occurs elsewhere on the surface of the body.

As suggested by Madden (1935), cutis verticis gyrata should be considered a descriptive term only, and it should be generally understood that several different pathologic processes in the scalp may result in the formation of convolutions and furrows. In any patient exhibiting cutis verticis gyrata, a careful differential diagnosis should be made to determine the underlying cause so that appropriate treatment can be recommended.

We believe that Masson has shown rather conclusively that a nevus represents a proliferation of the chromatophores, tactile corpuscles and nerve cells, forming the end-apparatus of the sensory nerve filaments of the skin. There seems to be little doubt of the relationship of the nevus to the neurofibroma. The results of the histopathologic study in the 2 cases herein reported support Masson's concept of the neurogenic nature of the nevus.

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FRACTURES OF THE ANKLE

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During the period from 1932 to 1934 there were admitted to the fracture service for females at the Cook County Hospital patients with 3,294 fractures. The fractures, dislocations and tears in the ligaments of the ankle numbered 352, or 10.84 per cent of all fractures. These were reduced and treated subsequently in the follow-up clinic. Our data are based on the records of the hospital and the follow-up clinic and on our study of 300 of the hospital's roentgenograms.

We are adding to these data the results of a study of 78 fractures of the ankle encountered in private practice, with a review of the roentgenograms. Our work, therefore, is based on a study of 430 fractures of the ankle and a review of the roentgenograms of 378.

The clinical study of these fractures has been augmented by a detailed description of the practical anatomy and physiology of the ankle joint by one of us (L. B.).

Even after employing the accepted methods of treatment of Pott's fracture and other injuries to the ankle, the results, such as faulty weight bearing, pes planus, limitation of motion, widening of the mortise and arthritic and circulatory changes, have motivated the study.

We propose to clarify confusion in the classification, anatomy and mechanism and to advocate an additional manipulation in the reduction of fractures with dislocation.

ANALYSIS OF DATA

The incidence of fractures of the ankle at the Cook County Hospital for the three year period was as follows:

	Total Fractures	Fractures of the Ankle	Percentage
1932	1,024	95	9.5
1933	1,070	99	9.2
1934	1,155	158	14.0
	3,249	352	10.84

On the basis of the type of fractures we classified the 300 fractures studied roentgenographically as follows:

	No.	Percentage
Pott's fracture (figs. 8, 9, 12, 13, 14, 15, 16, 17 and 22)	225	75.0
Supination fracture (fig. 19)	15	5.0
Bimalleolar fracture (fig. 10)	28	8.5
Solitary marginal fracture	3	1.0
Compression fracture (fig. 11)	5	1.6
Simple fracture (fig. 20)	21	7.3
Epiphysial separation (fig. 18)	3	1.0

We further subdivided the fractures of the ankle as follows:

A. Pott's fracture			225
Uncomplicated (figs. 8, 9, 15, 16, 17 and 22)		157	
With a Tillaux fragment (small marginal fracture)		27	
Anterior (fig. 14)	1		
Posterior (fig. 15)	24		
Anterior and posterior	2		
Anterior marginal		6	
Posterior marginal (fig. 12)		30	
Anterior and posterior marginal (fig. 23)		5	
B. Supination fracture			15
Uncomplicated (fig. 19)		9	
With a Tillaux fragment (posterior)		1	
Anterior marginal		2	
Posterior marginal		0	
Anterior and posterior marginal		1	
With fracture heads of the fibula		1	
With epiphysial separation		1	
C. Bimalleolar fracture (fig. 10)			28
Uncomplicated		20	
With a Tillaux fragment		0	
Anterior marginal		1	
Posterior marginal		6	
With epiphysial separation		1	
D. Solitary marginal fracture			3
Anterior		0	
Posterior (2 without dislocation)		3	
E. Compression fracture (fig. 11)			5
F. Simple fracture one or both maleoli (without any dislocation)			21
External malleolus (fig. 20)		17	
Internal malleolus		3	
External malleolus and anterior marginal		1	
G. Epiphysial separation (fig. 18)			3

In the roentgenograms of 300 fractures of the ankle we noted the following involvement of the bones:

External malleolus	150
Internal malleolus	109
Both malleoli	57
Fibula, above the joint	183
Oblique fracture of the fibula	153
Posterior marginal fragment	39
Anterior marginal fragment	9
Both Tillaux and marginal fragments	63
Tillaux fragment (posterior)	27
Both anterior and posterior marginal fragments	3

It is interesting to note the following facts:

1. Pott's fracture occurred in 75 per cent of our series but was complicated by some form of marginal fragment in 30 per cent. We consider this complication higher in females than in males, probably because the former wear high heels.

2. Solitary marginal fracture is uncommon, occurring only 3 times in 300 roentgenograms and from our records of 352 cases. This is less than 1 per cent of fractures of the ankle. In only 1 of these was there a posterior dislocation, so that 2 of these might have been classified as simple fractures.

3. The most common fracture was Pott's fracture, in which there is an oblique and sometimes a spiral fracture of the fibula running downward and forward. This constituted 50 per cent of all our fractures. It is the most common fracture of the ankle. In about 10 per cent of these there was also involvement of the external malleolus.

4. In supination or fractures with medial dislocation, we noted in addition to fracture in the fibula or external malleolus a longitudinal fracture of the tibia or a spiral fracture in the shaft of the tibia.

The incidence of dislocations was as follows:

Lateral dislocation	157
Posterior dislocation	45
With lateral and posterior dislocation	36
Upward dislocation (compression)	5
No dislocation	21
Reduction of fracture before taking roentgenogram (mostly Pott's fracture)	36
Diastasis noted roentgenographically	117

The clinical facts in this series of fractures are summarized briefly:

The time of fixation for uncomplicated Pott's fracture averaged five and one-half weeks; for lateral and posterior displacement, seven weeks; for all types, six weeks.

Two or more reductions were required in 30 cases.

There were 6 compound fractures. In 2 of these cases extension on a Braun or Böhler splint was used.

Extension with a Kirschner wire or a Steinmann pin was used 6 times.

The length of time before weight bearing was allowed averaged in all cases about ten weeks; for uncomplicated Pott's fracture, eight weeks; for Pott's fracture or bimalleolar fracture with posterior dislocation, eleven weeks; for posterior marginal fractures, eleven and one-half weeks.

Results were markedly good in 168 fractures, fair in 33, poor in 15 and undetermined in 84. These data depend entirely on the examiner's opinion. Measurements made by one of us on 50 fractures of the ankle showed an increase in the circumference of the ankle at the malleoli in 47. Note that in 300 roentgenograms diastasis was found in only 117, or 40 per cent, whereas widening of the mortise was observed in 94 per cent as a clinical end-result. In many of these there was pes planus, and in many others the roentgenograms showed fairly good position.

In reviewing the films and records of 78 cases encountered in private practice, we note the following distribution of fractures:

	No.	Percentage
Pott's fracture	38	49.0
Supination	2	2.5
Bimalleolar fracture	6	7.0
Solitary marginal fracture	2	2.5
Compression fracture	1	1.3
Simple fracture	29	37.0
Epiphysial separation	0	0.0

In this series, as compared with those at the Cook County Hospital, there were more uncomplicated Pott's fractures and more simple fractures. In the 2 posterior marginal fractures there were no posterior dislocations.

In looking over the films we found a single instance of injury to the ankle, clinically accompanied by swelling and pain but no fracture. There were, however, considerable diastasis and widening in the mortise. We found no cases of dislocation without fracture. Diastasis probably occurs in many cases of sprain and is a cause of later disability.

There were 21 multiple fractures in our series.

ANATOMY AND PHYSIOLOGY OF THE ANKLE JOINT

Only such anatomic points will be presented as bear on our views of the mechanism of fractures of the ankle.

Inferior Tibiofibular Syndesmosis.—The distal extremities of the tibia and fibula articulate by surfaces which are for the most part rough and bound together by ligament, but at the distal part, for a distance of about ¼ inch (0.6 cm.), they are separated by a cleft, continuous with the cavity of the ankle joint, which is lined by synovial membrane and commonly contains a synovial fold.

The ligaments of this articulation are: 1. The anterior lateral malleolar (anterior inferior tibiofibular) ligament (fig. 1). This ligament extends obliquely downward and outward, is about ¾ inch (1.9 cm.) wide and is attached to the external and anterior angle of the lower extremity of the tibia; it is attached to the fibula along the lower ½ inch (1.3 cm.) of the ridge in front of the superficial triangular surface of the bone; to the anterior surface of the malleolus, nearly down to the anterior portion of the external lateral ligament of the ankle, and to a part of the anterior ligament of the ankle. The fibers of the ligament increase in length from above downward.

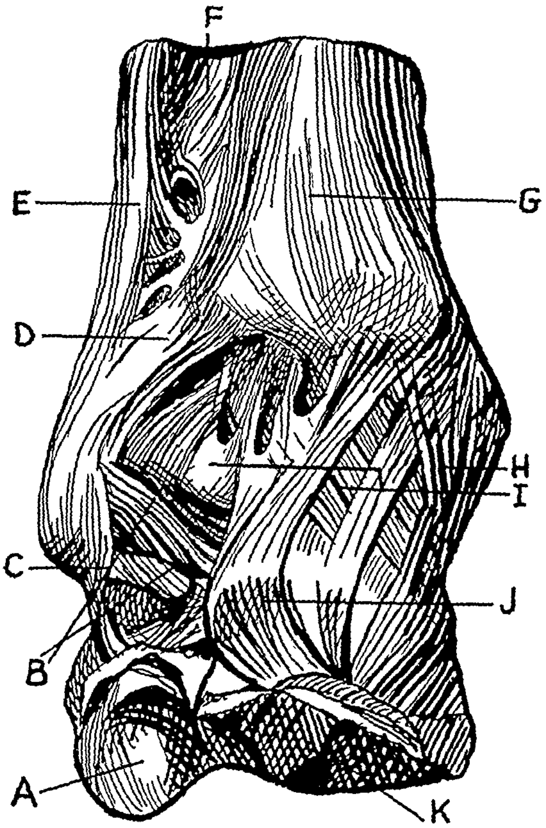

Fig. 1.—Anterior view of the ankle joint (*modified after Bourgery: Traité complete de l'anatomie de l'homme comprenant de la médicine operatoire*, Paris C.-A. Delaunay, 1832-1854). *A* indicates the calcaneum; *B*, two bands of the anterior talofibular ligament; *C*, the exterior lateral ligament; *D*, the anterior inferior tibiofibular ligament; *E*, the fibula; *F*, the interosseous ligament; *G*, the tibia; *H*, the internal lateral ligament; *I*, the anterior ligament of the ankle joint; *J*, a prominence formed by the astragalus, and *K*, the scaphoid.

2. The posterior lateral malleolar ligament (fig. 2). This ligament extends from the external angle of the posterior surface of the lower end of the tibia, downward and outward to the fibula, along the lowest ½ inch (1.3 cm.) of the ridge separating the posterior from the external surface and to the upper half of the posterior border of the external malleolus.

3. The transverse ligament (fig. 2). The posterior lip of the tibial plafond projects so low as to have been called by Destot the posterior malleolus. The transverse tibiofibular ligament, located beneath the posterior inferior tibiofibular ligament, extends from the posterior lip of the tibia to the posterior and inner angle of the base of the external malleolus. Another way of describing this ligament is that the distal part of the posterior inferior tibiofibular ligament forms a strong band, which takes a transverse course and is firmly attached to both the tibia and the fibula. It constitutes a part of the tibiofibular

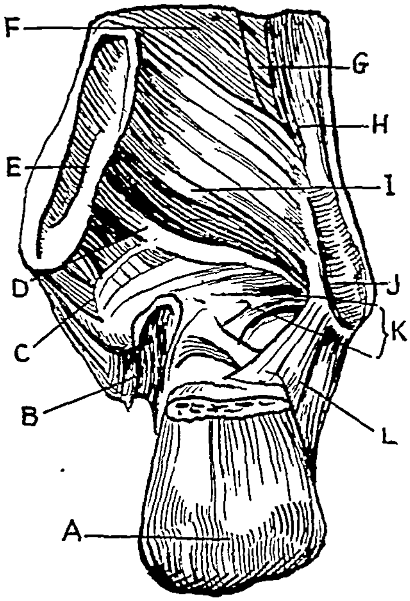

Fig. 2.—Posterior view of the ankle joint (modified by Bourgery). *A* indicates a posterior tubercle of the os calcis; *B*, a groove on the astragalus for the flexor hallucis longus tendon; *C*, the internal lateral ligament; *D*, the transverse ligament; *E*, a groove for the flexor digitorum longus and the tibialis posterior tendons; *F*, the tibia; *G*, the inferior interosseous ligament; *H*, the fibula; *I*, the posterior inferior tibiofibular ligament; *J*, a groove for the peroneus tendons; *K*, the posterior fasciculi of the external lateral ligament, and *L*, the middle fasciculus of the external lateral ligament.

socket for the talus at the ankle joint and is sometimes called "the distal ligament of the lateral malleolus."

4. The *inferior interosseous* ligament (figs. 1 and 2). This ligament consists of a dense mass of short fibers, passing transversely between the opposed lower ends of the tibia and the fibula, except for ⅜ inch (0.9 cm.) at the extremity of these surfaces, where there is a synovial cavity. The ligament extends from the anterior to the posterior inferior tibiofibular ligaments. In front it reaches upward for 1½ inches (3.8 cm.), but behind, only about half that height.

The synovial cavity of this articulation communicates with that of the ankle joint. It is semilunar, with its convexity upward, where it is limited by the lower end of the inferior interosseous ligament.

The Ankle Joint Proper.[1]—This is a hinge joint, and the distal extremities of the tibia and the fibula are united so as to form a three-sided socket, which receives and embraces the talus. The socket is completed opposite the interval between the tibia and the fibula by the lower part of the anterior lateral malleolar ligament (mentioned previously) in front and by the transverse ligament behind. It is broader in front than behind, and its posterior margin is placed on a lower level than the anterior margin. An irregular archway is thus formed by the two bones of the leg, under which is received the astragalus, the outer buttress, which is the longer, being formed by the fibula, while the inner buttress and the span of the arch are formed by the tibia.

Ligaments of the Ankle Joint.—A capsular ligament invests the joint; it is thin in front and behind but is supported on each side by strong collateral ligaments. This capsular ligament, being attached in places beyond the astragalus, assists in forming the capsules of some of the tarsal joints. There are four named ligaments: the anterior, posterior, internal and external lateral.

The anterior and the posterior ligaments need no description.

The internal lateral ligament [2] (fig. 3), erroneously named the deltoid ligament, is a quadrilateral mass of vertical, coarsely fasciculated fibers, descending from the tibia to be attached posteriorly to the astragalus and anteriorly to the sustentaculum tali. The anterior part of this ligament is strengthened by fascia (partly derived from the internal annular, or laciniate, ligament), which fashions it into a deltoid structure. After reaching the sustentaculum tali, the true ligamentous fibers interlace with the upward and forward passing fibers of the superointernal calcaneonavicular ligament.

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[1] Lovett, R. W., and Cotton, F. J.: Some Practical Points in the Anatomy of the Foot, Tr. Am. Orthop. A. **11**:298-315, 1898.

[2] Smith, E. Barclay: The Astragalo-Calcaneo-Navicular Joint, J. Anat. & Physiol. **30**:397, 1895-1896.

The external lateral ligament (fig. 4) consists of three parts. (*a*) The anterior portion is connected with the anterior border of the external malleolus just below the point of attachment of the anterior ligament of the ankle. Below it is fixed to the astragalus in front of the facet for the fibula. (*b*) The middle fasciculus is attached to a portion which passes as a groove round the inferior border of the external malleolus, slightly in front (but not to the tip), and passes downward to a tubercle on the outer surface of the os calcis. (*c*) The posterior fasciculus, probably the strongest of all, is attached at one end to the border of the external malleolus, which separates the peroneal groove

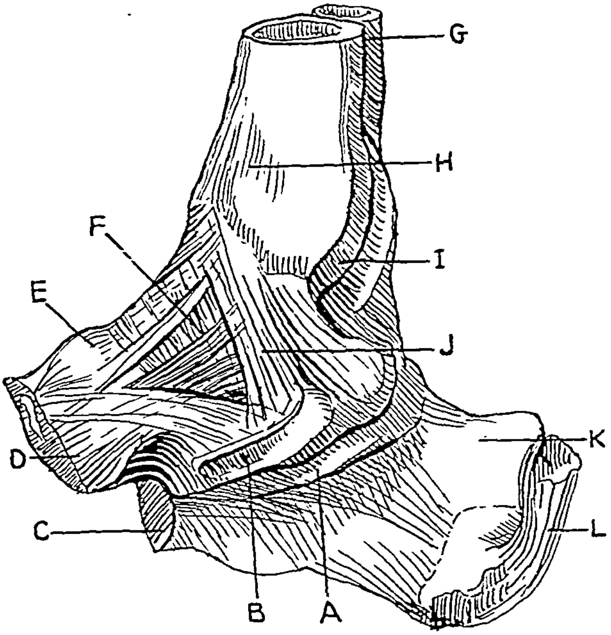

Fig. 3.—Medial aspect of the ankle joint (modified after Bourgery). *A* indicates the groove for the flexor digitorum longus and the flexor hallucis longus tendons; *B*, the groove for the tibialis posterior tendon; *C*, the calcaneus; *D*, the scaphoid; *E*, the astragalus; *F*, parts of the internal lateral and anterior ligaments of the ankle joint; *G*, the fibula; *H*, the tibia; *I*, the groove on the tibia for the flexor digitorum longus; *J*, the interior lateral ligament; *K*, the calcaneum, and *L*, the tendo Achilles.

from the fossa on the inner surface, and slightly to the lower part of the fossa itself, and at the other end to the rough outer surface of the astragalus below and to the articular facet for the fibula behind and also to the posterior external tubercle of the astragalus. This groove and depression for the posterior fasciculus constrict and weaken the bone. In accidents, because of the enormous strength of this posterior fasciculus, holding the astragalus almost indissolubly attached to the external malleolus, either the fibula gives way, which is usual, or the posterior tubercle of the astragalus is detached. This lateral tubercle of the posterior process of the astragalus, or os trigonum, is present as a distinct bone or additional ossifying center in 7 or 8 per cent of cases. It is located from 5 to 7 mm. posterior to the median tubercle and is the portion of the astragalus which casts the farthest posterior shadow in lateral roentgenograms of the foot.

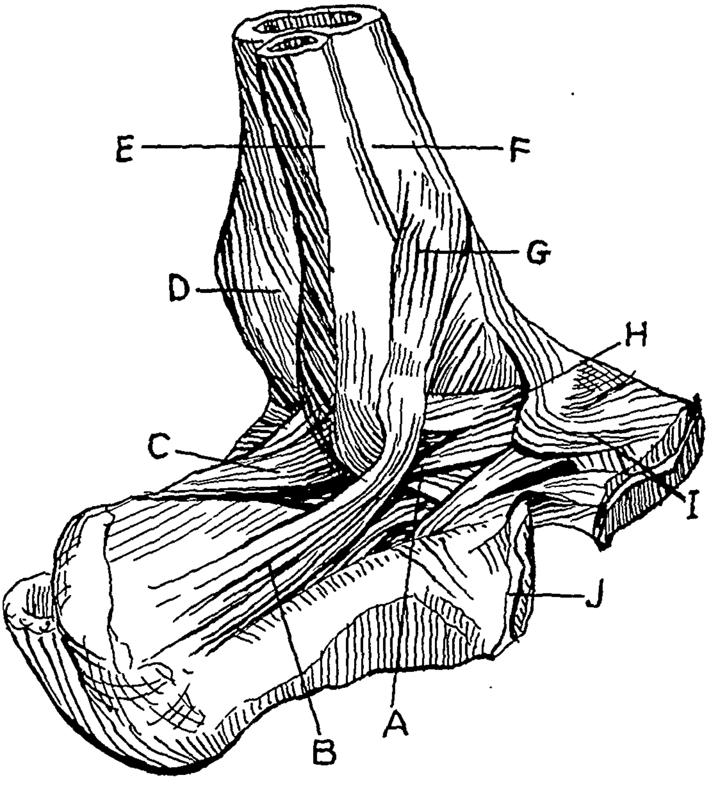

Fig. 4.—Lateral view of the ankle joint (modified after Bourgery). *A* indicates two bands of the anterior talofibular ligament; *B*, the middle fasciculus of the external lateral ligament; *C*, the posterior band of the external lateral ligament; *D*, the tibia plus part of the posterior inferior tibiofibular ligament; *E*, the fibula; *F*, the tibia; *G*, the anterior inferior tibiofibular ligament; *H*, the anterior band of the exterior lateral ligament; *I*, the scaphoid, and *J*, the calcaneum.

The synovial membrane of the ankle joint is extensive. It lines all the ligaments and sends upward a short cul-de-sac for the inferior tibiofibular joint. On the anterior and posterior surfaces it extends beyond the limits of the articular facets. The epiphysial line of the tibia is ½ inch (1.3 cm.) above the level of the ankle joint in front and about ⅝ inch (1.5 cm.) above posteriorly, so that the synovial membrane does not reach this line on either aspect. The epiphysial line of the fibula is from ¾ to ⅞ inch (1.9 to 2.1 cm.) above the tip of the external malleolus and is almost 1 cm. below that of the tibia, lying in a direct horizontal line with the opposed articular surfaces of the tibia and the astragalus. This epiphysis, then, lies almost exactly on a level with the plane of the ankle joint. The synovial membrane overlaps the diaphysis of the fibula for about 0.5 cm.

Bony Configuration.—(*a*) Lower End of the Fibula: The external malleolus supports the ankle joint on the outer side, projecting down and more posterior than the internal malleolus. The result of this is that the foot may receive, in the best possible way, shocks transmitted to it from above.

(*b*) Shaft of the Tibia: This part of the bone is twisted; when the tibia is placed on its posterior surface it rests on the posterior edges of both its condyles but on the posterior and lateral edges only of its lower articular end, the inner malleolus being turned away from the supporting surface. This twist in the tibia gives an outward slant to the foot from the heel, causing the great toe to incline away from that of the opposite side when the heels are placed in contact. A line drawn from the point of the heel through the middle or longest toe coincides with the plane in which the foot moves in flexion and extension on the leg. The direction of this movement, therefore, is oblique with regard to that of the knee joint and to that of the plane in which the leg bones descend from the knee. The movement of the ankle joint takes place in a perpendicular plane on an axis, which passes from left to right through the lower part of the astragalus and which is the center of a circle of which the upper articular surface of the astragalus forms a segment.

(*c*) Astragalus: The whole of the upper, outer and inner surfaces and the greater part of the posterior surface of this bone assist in forming the ankle joint, either by smooth cartilaginous facets for articulating with the bones of the leg or by rough surfaces for the attachment of the ligaments. Of the three facets, we shall consider the superior only for our present purpose. This occupies the posterior two thirds of the upper surface of the bone; it is arched considerably, being decidedly narrower behind than in front and longer on the inner than on the outer side; the outer border is higher and more prominent, especially in front, so that there is a slight inward obliquity given to this upward looking facet.

From this description the fact can be appreciated that in extreme extension, or plantar flexion, there is a twisting of the toes inward and that is partly due to: (1) the greater posterior length of the inner border of the superior articular surface of the astragalus; (2) the lesser proportionate height posteriorly of the outer border of that surface, the hindmost part of which is in plantar flexion brought into the tibiofibular arch, and (3) also partly the lateral movement in the calcaneo-astragaloid joints.

The movements of the foot on the leg are varied and difficult to analyze, because they pass easily into one another; because, as Humphry[3] stated, two or more are generally combined, and because they are divided between three distinct joints. These are (1) the joint between the tibia, fibula and astragalus; (2) the joint between the astragalus and the os calcis, a double joint having two separate synovial cavities, and (3) the joint between the first and the second row of tarsal bones—between the astragalus and the os calcis behind and the scaphoid and the cuboid bone in front—which is also a double joint.

Flexion and extension at the ankle joint take place around a transverse line drawn through the body of the astragalus. The movements are not in a direct anteroposterior plane but along a plane inclined outward and drawn through the foot from the middle of the astragalus to the opposed surfaces of the bases of the second and third metatarsal bones. This oblique plane corresponds to the outward inclination of the toes, to the slight twisting of the shaft of the tibia and to the posterior position of the external malleolus. For the sake of brevity we may say that the axis of movement of the ankle joint passes approximately through the end of the fibular malleolus. Thus the middle fasciculus of the external lateral ligament can be more or less tense throughout the range of movement, but the anterior and posterior fasciculi, being attached to the fibula away from the axis, are of more value in limiting movement and become tense in plantar flexion and dorsiflexion, respectively.

There is a slight lateral movement of the foot in ordinary plantar flexion, owing partly to the fact that the internal malleolus is shorter than the external and partly to the narrower end of the astragalus being in that position brought into the widest part of the intermalleolar notch.

Muscles Acting on the Ankle (Directly or Indirectly).—It is well known that no single muscle can produce simple flexion or extension of the foot without producing abduction or adduction at the same time.

1. The gastrocnemius and the soleus (spoken of together as the triceps surae) are the extensor-adductor muscles. They act by stretching the back part of the foot and the outer half of the forepart of the foot; they act in the plane of movement of the ankle by means of the tendo Achillis, which plane may, for simplicity, be said to be passing through the os calcis, the middle of the ankle joint and the space between the two inner metatarsal bones.

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[3] Humphry, G. M.: A Treatise on the Human Skeleton (Including the Joints), Cambridge, Macmillan & Co., 1858.

2. The peroneus longus is the extensor-abductor muscle; the action of this muscle, combined with that of the triceps surae, causes direct extension of the foot at the ankle.

3. The tibialis anticus is the flexor-adductor muscle.

4. The extensor digitorum longus is the flexor-abductor muscle; the action of this muscle, combined with that of the tibialis anticus, causes direct flexion of the foot.

5. The tibialis posticus is a pure adductor muscle.

6. The peroneus brevis is a pure abductor muscle.

However, as pointed out by Cyriax (1917), Haines (1935) and others, some muscles have full action and others short action; the latter are those in which the length of the fibers is so short that they do not remain taut throughout the full range of movement permitted by their attachments; these include the biceps femoris, semimembranosus, rectus femoris, gastrocnemius, plantaris and soleus muscles. For example, when the ankle is in full plantar flexion and the knee is also flexed, the lower part of the leg not touching the ground, the tendo Achillis is slack to palpation. The only active muscles appear to be the tibialis posticus and peroneus muscles.

NOMENCLATURE OF THE MOVEMENTS OF THE ANKLE AND FOOT

There is a good deal of diversity of opinion concerning the nomenclature of the movements of the ankle and foot. We fully concur with the contention of Professor Thane,[4] who claimed that although the foot in the position of rest is more or less at right angles with, and projects both in front of and behind, the bones of the leg, the two projections are not of equal value. The axis of the limb is continued in the anterior projection, and the projection of the heel is a secondary prominence, which does not occur in the primitive form. The angle between the leg and the forepart of the foot is, therefore, the angle to be considered. A diminution of this angle is flexion, and an increase of this angle is extension, in accordance with what would universally be understood by "straightening the foot upon the leg." The terms flexion and extension are physiologic terms, and it is desirable that they should be used only in a physiologic sense. The direction at which the bending at a given joint takes place is determined by the functional requirements of the part. In the upper limb all the joints are bent in the same direction, in accordance with the use of the limb as a grasping organ. In the lower limb the large joints are bent in opposite directions alternately, that arrangement being the most convenient for the shortening of a column of support. We therefore conclude with most authorities that plantar flexion is extension of the foot and dorsiflexion, flexion of the foot.

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[4] Thane, G. D., in discussion on Humphrey, G. M.: J. Anat. & Physiol. **28**:xv-xvi, 1893-1894.

Other movements are described in connection with the ankle and foot; these, however, belong not to the ankle but to the subastragaloid joints.

The movements of pronation of the foot consist of the horizontal rotation of the astragalus with the sinking of its head, the rotation in valgus of the os calcis beneath it and the rotation in valgus and abduction of the front part of the foot as a whole, occurring between the astragalus and the scaphoid and between the os calcis and the cuboid bone. The head of the astragalus moves in a ball and socket joint formed by the sustentaculum tali, the calcaneoscaphoid ligament and the scaphoid. It moves inward and backward toward the sole, and this is accompanied by the very oblique change in position of the malleoli, which, of course, move with it in this rotation, the inner malleolus backward and the outer malleolus forward. As the foot is supinated, there is a movement downward of the scaphoid over the head of the astragalus as well as a movement inward.

An important question may now be brought up in connection with this discussion. During the execution of flexion and extension in a seemingly simple ginglymoid diarthrosis like the ankle joint, what is the function of the fibula? Does it possess much elasticity; does it move, and if so, how and where?

We shall mention the opinions of several investigators, beginning with Humphry,[3] who stated:

> It is not enough to say that the socket of the leg bones is shaped in conformity with this configuration of the articular surface of the astragalus. For, if that had been all, and if the fibula had, like the inner malleolus, formed a part of the tibia so that the socket had been hollowed out of the solid bone and had maintained an unvarying size, it could not have been adapted to the astragalus in the different positions of the limb. It would have either been too large when the joint was *extended* or too small when it was *bent*. But the outer malleolus, being a little movable, permits a slight alternate widening and narrowing of the socket in flexion and extension; so that freedom of movement is combined with the maintenance of an exact coaptation of the articular surfaces. This yielding of the outer malleolus in a lateral direction, under the pressure of the articular surface of the astragalus during flexion, and its recoil in extension depend not so much upon a yielding of the ligaments that bind it to the tibia as upon the elasticity of the bone itself. Hence a careful examination will show that during flexion, when the malleolus is pressed outward, the shaft of the fibula is, at its narrowest part, just above the ankle, bent a little inwards; and vice versa, when the joint is extended, the shaft recoils to its former distance from the tibia.

Ashhurst[5] stated that Nancrede called Humphry's theory "preposterous and untrue." We cannot find any references about that remark. We believe that these are Ashhurst's own words. In the first place, Nancrede was not aware of the work and teaching by Miles and Humphry some twenty years before him. Nancrede[6] merely answered an attack on him for plagiarism by Dr. Randolph Winslow. Dr. Winslow pointed out to him that all this was known and taught by others. However, Nancrede stated that a little reflection would demonstrate the mechanical impossibility of Humphry's view about the yielding of the external malleolus in a lateral direction during flexion and its recoil in extension.

Nancrede,[7] in another article, went on to explain his views, for a part of which he justly claimed originality.

> . . . all the ligamentous fibers pursue an *oblique course from the tibia downward to the fibula,* and that the capsule of the superior tibio-fibular joint is a loose one.
>
> The diagram [fig. 5] will show the course pursued by the fibers . . . the apposed rough surfaces of the inferior tibio-fibular joint are connected by a short, felt-like collection of fibrous tissue—i. e., the inferior interosseous ligament.
>
> . . . the ligaments must be perfectly inextensible and inelastic to perform their functions properly.
>
> A little reflection will demonstrate that, in walking, the moment the foot is placed upon the ground the body still tends to go forward from its own impetus, and there is a marked tendency for the leg bones to slip forward upon the dorsum of the foot. This is not theory, but a demonstrable fact. Some provision against this must be made. If the immunity from displacement had to depend on the posterior ligament of the ankle-joint, it would have to be enormously strong. But let it never be so strong, unless it were *tight* it would not prevent luxation. If, however, it were tense in all positions where this forward displacement was liable to occur, it *would render flexion utterly impossible.* What, then, *is* the arrangement found? Simply that the astragalus is wedge-shaped, with its base in front, so that the more the leg bones tend to slip forward the tighter the articular surfaces are pressed together. This also is not theory, but a simple mechanical fact. The shape of the bony surface—excluding the muscles, which, as is too commonly overlooked, are often the most important ligaments of a joint—is absolutely the only obstacle worth mentioning to forward displacement of the leg bones. . . .

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[5] Ashhurst, A. P. C., and Bromer, R.: Classification and Mechanism of Fractures of the Leg Bones Involving the Ankle, Arch. Surg. **4**:50-129 (Jan.) 1922.

[6] Nancrede, C. B.: An Answer to Dr. Randolph Winslow's "Reply" to Dr. Nancrede's Paper upon the Tibio-Fibular and Ankle Joint, Maryland M. J. **7**: 76-78, 1880.

[7] Nancrede, C. B.: Some New Observations upon the Anatomy and Functions of the Ankle and Tibio-Fibular Joints, Philadelphia M. Times **10**:316-318 (March 27) 1880.

This shape, however, of the astragalus and its socket, if the latter were rigid, would completely arrest flexion, as the broad anterior end, already firmly embraced by the malleolar arch, could not be made to pass backward into the still narrower portion of the socket, as is actually the case in flexion. . .

How, then, is an *adaptable* socket provided? Simply by having *two* bones in the leg, *one of which is movable*, the other fixed. By examining the diagrams it will be seen that the tibia and fibula can be compared to the two halves of a parallel ruler, and the ligamentous fibers to the two brass arms of the same instrument. Both the ligament and the brass arms are inextensible, but any wedge-like object insinuated between the two halves will push up the movable half and widen the space between them.

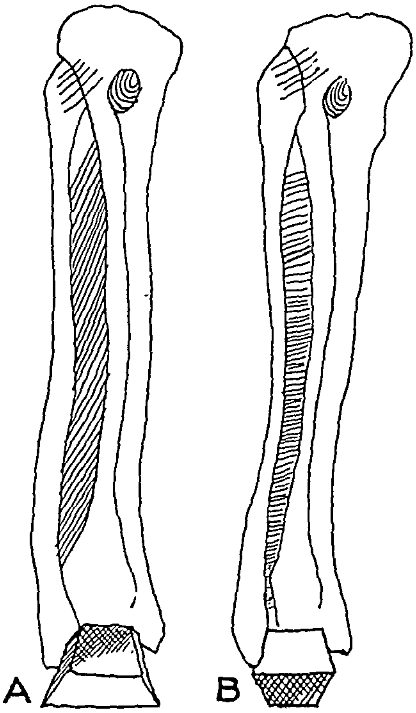

Fig. 5.—Direction of the fibers of the lower part of the interosseous membrane in extension (*A*) and flexion (*B*) of the foot.

Just so in the ankle-joint. In extreme extension [fig. 7] the narrow part of the astragalus is carried forward to that part of the socket which before accommodated the wide portion of that bone; and yet there is complete apposition of the bony surfaces, because the movable bone—i. e., the fibula—glides down. Again, in flexion the wide anterior portion of the astragalus is pressed between the narrower portion of the socket, which is widened by the fibula gliding *upward*. This upward gliding approximates the attachment and origin of the ligamentous fibers just enough to permit the two malleoli to be sprung apart sufficiently to admit the base of the astragaloid wedge. From the mode of attachment of the middle band of the external lateral ankle ligament—viz., in front and above the apex of the internal malleolus [he meant external malleolus]—this structure is tense in every position of the joint, and especially in extension winds around the malleolus, thus pulling it down and narrowing the socket in the extended position when such a condition of the malleolar arch is demanded.

From the foregoing statement it is apparent that Nancrede should claim originality for his views about the gliding upward and downward of the fibula.

NOTE.—In our brief communication on the structure and function of the ankle joint, the universally accepted views have been put forth as a matter of simplicity. These views are shared to a great extent by the original researches of von Meyer, Langer, Henke, Heuter, Meissner, Goodsir and others. Mr. W. Arbuthnot Lane, however, making an independent and exhaustive examination of the ankle joint in 1888, offered views on this subject, some of which differ materially from those mentioned in our review. The latter author called attention to the following facts:

(*a*) One must examine the astragalus in the recent state and not as a dry bone; one will then observe a "ligamentous facet" or "triangular area" as being cut off from the posterior and outer part of its upper surface; it is nonarticular; during flexion the posterior ligament, together with the posterior inferior tibiofibular and the posterior portion of the external lateral ligament, rests and plays on the triangular area.

(*b*) Also, during flexion of the ankle, the ligaments which are chiefly engaged in preventing the separation of the malleoli by the wedge-shaped internal articular surface of the astragalus are: the anterior inferior tibiofibular ligament, the posterior fasciculus of the external lateral ligament and the back part of the deltoid ligament. The interosseous membrane, the posterior inferior tibiofibular ligament and the inferior interosseous ligament take but a secondary share in this work.

(*c*) In complete extension of the ankle joint the concavity on the projection on the back of the astragalus comes into contact and articulates with the corresponding little articular surface on the tibia and with the adjacent portion of the posterior inferior tibiofibular ligament; the impact of these two opposing surfaces limits the movement of extension. In this position the only other articular surfaces in contact with each other are the outer articular surface of the talus with the corresponding facet on the outer malleolus.

(*d*) The transverse ligament is but a portion of the posterior ligament of the ankle joint. This posterior ligament is a distinct and important structure. It is attached externally to the fibula in the interval between the attachments of the posterior inferior tibiofibular ligament and the posterior fasciculus of the external lateral ligament. It consists of radiating fibers which cover in the ankle joint posteriorly. The upper margin of this ligament is practically continuous with the posterior inferior tibiofibular ligament and its lower limit with the posterior fasciculus of the external lateral ligament.

(*e*) The posterior fasciculus of the external lateral ligament limits and opposes movements both of complete flexion and of complete extension of the ankle joint, for the reason that its fibers occupy a horizontal plane and the interval between its points of attachment is least where the joint occupies a position midway between complete flexion and extension. Any deviation from this posture renders the fibers oblique.

(*f*) The same author maintained, therefore, that in any degree of flexion or extension of the ankle the head of the astragalus cannot be displaced inward owing to the strain exerted on it in an outward and backward direction by the anterior fasciculus of the external lateral ligament. It cannot be displaced outward on account of the strain exerted on it by the anterior portion of the deltoid ligament in a backward and inward direction.

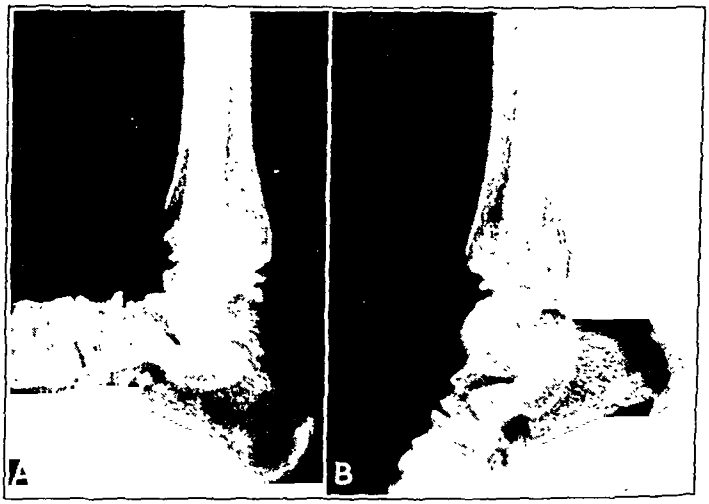

Fig. 6.—*A*, descent of the fibula in plantar flexion; *B*, ascent of the fibula in dorsiflexion.

REVIEW OF THE LITERATURE

In 1756 Sir Percival Pott suffered a compound fracture of both bones of the lower part of the leg, which resulted not only in his survival but in the repair of the fracture and later in 1768 in a description of "Pott's fracture." We refer the reader to this interesting and sparkling treatise in a compilation by Sir James Earle, "The Chirurgical Work of Sir Percival Pott, with Observations."[8]

We were not only regaled by this description but by the good judgment shown by Sir Percival when he refused to be transported from the site of the accident until the leg had been immobilized, a principle in treatment of fractures which is neglected by the modern surgeon and the attendant of the police ambulance.

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[8] Pott, Percival: The Chirurgical Works of Percival Pott, Philadelphia, J. Webster, 1819, pp. 246-252.

Pott, in his treatise, pointed out the power which the peroneus muscles acquire in consequence of the loss of support occasioned by fracture of the fibula and the resulting eversion and elevation of the foot.

Preceding and following Pott up to the time of Sir Astley Cooper[9] and Dupuytren[10] were several interesting writers, among whom we may mention Petit[11] (1723), Bromfield[12] (1773), Pouteau[13] (1783), Castella[14] (1808) and Bell[15] (1809).

Cooper[9] (1830-1840) seems to have had an appreciation of the various dislocations, including posterior displacement, which occurs in posterior marginal fracture.

Dupuytren[10] (1830-1840), in a masterful treatise on "Fractures of the Fibula", in which he reported 207 cases with 5 deaths, specially pointed out the ligament tears, the result and the fact that dislocation of the foot at the ankle joint does not occur without fracture.

We now come to Maisonneuve[16] (1840), who described lateral dislocation of the foot with high fibular fracture, now known as the Maisonneuve fracture, and presented an interesting discussion on the mechanism of injuries to the ankle. He was first to point out the importance of the tibiofibular diastasis which we are emphazing in this paper.

In 1879 Tillaux[17] discussed fractures of the ankle, and the so-called "third fragment" was introduced.

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[9] Cooper, A. P.: A Treatise on Dislocations and Fractures of the Joints, edited by B. B. Cooper, Philadelphia, Blanchard & Lea, 1851, pp. 246-298.

[10] Dupuytren, Gillaume: On the Injuries and Diseases of Bones, translated and edited by F. le Gros Clark, London, New Sydenham Society, 1847, pp. 234-315.

[11] Petit, Jean-Louis: Traité des os: Dans lequel on a représenté les appareils et les machines qui conviennent à leur guérison, Paris, C.-E. Hochereau, 1723.

[12] Bromfield, W.: Chirurgical Observation and Cases, London, T. Cadell, 1773.

[13] Pouteau, Claude: Oeuvres posthumes, Paris, P.-D. Pierres, 1783.

[14] Castella, M.: Essai sur les fractures du péroné, Landshut, J. Thomann, 1808.

[15] Bell, Charles: A System of Operative Surgery, Founded on the Basis of Anatomy, ed. 2, London, Longman [and others], 1814, pp. 363-365.

[16] Maisonneuve, J. G.: Recherches sur la fracture du péroné. Arch. gén. de méd. **1**:165-187 and 433-473, 1840.

[17] Tillaux, Paul: Traité d'anatomie topographique avec applications à la chirurgie, Paris, Asselin & Houzeau, 1879.

Hoenigschmied[18] in 1877 made some exceedingly interesting studies, 125 in all, on cadavers to determine the mechanism of fracture of the ankle.

Bondet in 1899 and Destot[19] in 1911 introduced physiologic classifications, adopted later by Quenu[20] and Tanton, both of whom used these classifications and added to theories in mechanism.

The mechanism of Pott's fracture was one of the favorite discussions in the clinics of Dr. John B. Murphy.[21] One of us remembers with what emphasis Dr. Murphy described the mechanism. He also recognized the importance of diastasis but denied the possibility of Pott's fracture occurring by inversion of the foot.

The advent of the x-rays has greatly enhanced our knowledge of the many combinations of fragments, of the dislocations and especially of the posterior marginal fragment and the arthritic changes which follow these fractures.

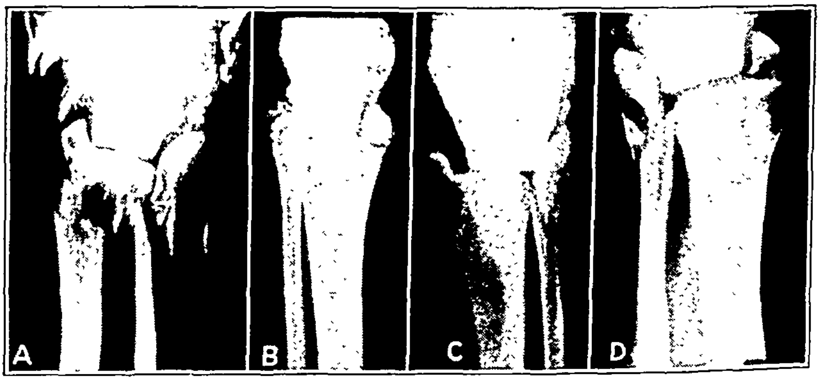

Fig. 7.—*A*, compression fracture; *B*, bimalleolar fracture; *C*, simple Pott's fracture without fracture of the internal malleolus, and *D*, simple Pott's fracture with an oblique fracture of the fibula above the malleolus and the internal malleolus—the common type.

Among the outstanding American writers are Kellogg Speed,[22] who published a report based on a study of 208 cases of Pott's fracture from from the Cook County Hospital, and Ashhurst and Bromer,[5] who reported 300 cases of fractures of the ankle, giving, perhaps, the most detailed classification with an interesting study of the literature.

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[18] Hoenigschmied, J.: Experimente über die Zerreissungen der Bänder im Sprunggelenk, Deutsche Ztschr. f. Chir. **8**:*239-260, 1877.*

[19] Destot, Etienne: Fractures de la région malléollaire, in Traumatismes du pied et rayons X, *1911,* pp. *75-134.*

[20] Quenu, E.: Plaies de pied et du cou-de pied par projectiles de guerre, Paris, F. Alcan, *1918,* pp. *185-190.*

[21] Murphy, J. B.: Pott's Fracture, Surg. Clin. **1**:451, 1912; Ancient Pott's Fracture: Operative Reduction; Nailing of Malleoli, *ibid.* **5**:*349, 1916.*

[22] Speed, Kellogg: A Discussion of Pott's Fracture with Complications, Based on a Series of Two Hundred Eight Cases, Surg., Gynec. & Obst. **19**:873-882, 1914.

The works of Cotton and Berg,[23] especially on posterior marginal fractures and on a classification according to dislocation, are important landmarks in the development of this subject.

We are also much interested in the fact that Bardenheuer advocated traction in the treatment twenty years ago, a fact which is now generally accepted by the German surgeons, especially Felsenreich[24] and L. Böhler, in the more serious types of fractures of the ankle.

Other interesting contributions have been made by Stimson, Stevens,[25] Shands,[26] Delbet, Robert,[27] Hubmann[28] and Pels-Leusden.

MECHANISM OF FRACTURES OF THE ANKLE

In considering the mechanism of the ankle joint, one notices that the column transmitting the weight of the body from the thigh to the foot consists of two bones, which are so united as to form a solid medium, the fibula gliding to a slight extent upward and downward during dorsiflexion and plantar flexion, respectively, allowing no lateral motion. The base of the column is the foot, but the ankle joint is not placed in the center of the weight-bearing arch of the foot. If a vertical line is dropped from the center of the base of the femur, it falls on the inner part of the astragalus, which is itself placed at the inner and posterior part of the foot. This accounts for the greater power of the adductor or supinator muscles. This line again divides the foot as regards its anterioposterior axis into two unequal portions, nearly three-quarters being in front of and one-fourth behind the center of gravity. It is well known, as pointed out by Osgood, that in the uninjured and healthy limb the adductor or supinator muscles exceed the pronator muscles in strength in the proportion of 5:4. But as soon as fracture of one of the bones of the lower part of the leg is produced, the ratio does

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23. Cotton, F. J., and Berg, R.: Ankle Fractures: New Classification and New Class, New England J. Med. **201**:753-760 (Oct. 17) 1929.

24. Felsenreich, Fritz: Untersuchungen über die Pathologie des sogenannten Volkmannschen Dreiecks neben Richtlinien moderner Behandlung schwerer Luxationsfrakturen des oberen Sprunggelenks, Arch. f. orthop. u. Unfall-Chir. **29**:491-529, 1931.

25. Stevens, James H.: Compression Leverage Fractures of Ankle Joint, Surg., Gynec. & Obst. **38**:234-252, 1924.

26. Shands, A. R.: Fracture-Dislocations of the Ankle: Analysis of Series of One Hundred Nine Cases, Internat. J. Med. & Surg. **42**:238-244, 1929.

27. Robert, Leslie: Treatment of Ankle and Leg Fractures by the "Delbet" Ambulatory Plaster Splint, Brit. J. Surg. **15**:414-429, 1928.

28. Hubmann, Paul: Ueber die Frakturen des obern Sprunggelenks mit besonderer Berücksichtigung der hinteren Luxationsfraktur und ihrer Behandlung, Beitr. z. klin. Chir. **147**:417-433, 1929.

not hold any more. The long and short peroneus muscles, assisted by some of the muscles lying in front of the ankle (the extensor digitorum longus and peroneus tertius), overcome the power of the adductor or supinator muscles and therefore evert the foot and help to produce a lateral dislocation.

For this reason we must forget previous conceptions that all Pott's fractures are produced by turning the foot outward and that turning the foot inward produces, when fracture occurs, always a medial dislocation.

Clinical experience is of no assistance, since most patients cannot remember whether they turned the foot outward or inward.

For this reason any classification on an etiologic basis is untenable; nor does the dislocation reveal the mechanism.

Some authors explain the mechanism entirely along mechanical lines, having in mind the weight-bearing axis, various levers, stress and strain. Under "Anatomy and Physiology of the Ankle Joint" we have shown that the movement of the foot is not in a direct anteroposterior plane but in a plane inclined outward and obliquely, owing to the outward inclination of the toes, to the slight twisting of the tibial shaft and to the posterior position of the external malleolus. This, plus other factors, such as the varying equinus position of the foot (females), genu valgum or varum, the weight of the body, the type of the shoe, the grade of the terrain and other extrinsic forces, all bring forth various factors in the mechanism of production, and, after all, interest us in the mechanism of this fracture more from an anatomic standpoint.

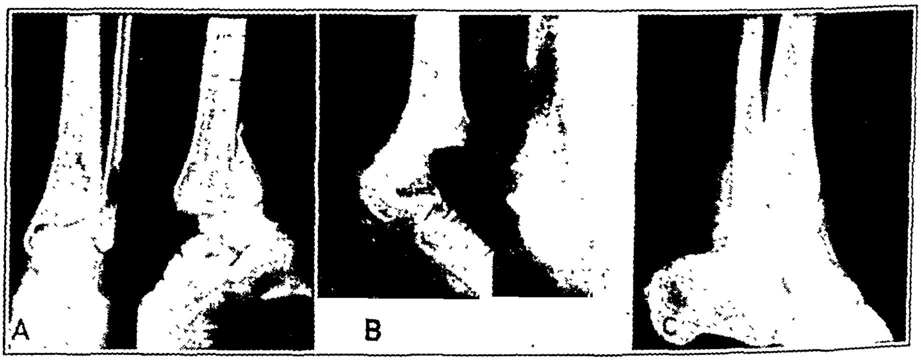

Fig. 8.—*A,* Pott's fracture with posterior marginal and posterior dislocation (a Cotton fracture); *B,* Pott's fracture with marked posterior dislocation but no posterior marginal fragment, and *C,* Pott's fracture with anterior chip (a *Tillaux* fragment).

Most writers in describing Pott's, or pronation, fracture have held the view that one of two lesions occur primarily. Stimson, Bonnet and Tillaux stated that the first lesion is the tear of the internal lateral ligament or the internal malleolus, which allows the tibia to move laterally and later to act as a fulcrum in fracturing the fibula. Murphy, Speed, Ashhurst and Maisonneuve stated that the astragalus in eversion of the foot acts as a fulcrum, first fracturing the fibula, and that the anterior inferior tibiofibular and the internal lateral ligament tear later in Pott's fracture.[25]

Maisonneuve in 1840 was the first to appreciate the rôle played by the inferior tibiofibular ligaments in the production of fractures of the ankle. Other writers have referred to the diastasis and the disability resulting therefrom.

Examination of leverage injuries of the ankle joint, whether sprain or Pott's fracture, invariably shows local tenderness slightly medial and inferior to the external malleolus, pointing to a lesion of the anterior inferior tibiofibular ligament (Aitken, 1934).

The collateral ligaments are the strongest ligaments of the ankle joint. The inferior tibiofibular ligaments, although resistant to force, are subject to constant strain in any position of the foot. This strain is accentuated by the up and down movement of the distal end of the fibula during flexion and extension. This fact, brought out in our anatomic discussion, has been previously overlooked to a great extent.

Measurements made after fracture-dislocations of the ankle joint show commonly a widening in the mortise due to diastasis of the tibiofibular articulation. Reference to our "Analysis of Data" shows this condition present grossly in 40 per cent of the roentgenograms. It is difficult, unless comparative roentgenograms are made, to determine a little diastasis.

The foregoing anatomic and clinical facts lead us to believe that the tear in the anterior inferior tibiofibular ligament with subsequent diastasis is not only a constant lesion in leverage injuries of the ankle joint, including sprains, Pott's fracture and other types of fracture, but that it is the primary lesion.

We know of no permanent way of proving our observations but feel that our views are fairly well founded on an anatomicopathologic basis, whereas the opinions of previous writers are only theories visualized on mechanical grounds.

In more severe violence the posterior inferior tibiofibular ligament and even the interosseous ligament may be torn, causing more marked diastasis.

After a tear in the tibiofibular ligament, it acts as a fulcrum, the degree of tear determining the site of fracture in the fibula. With a tear in the interosseous ligament, the fracture is high on the fibula, as described by Maisonneuve.

The tear in the anterior inferior tibiofibular ligament is followed by a tear in the internal lateral ligament, and this, together with the up and down movement of the fibula, allows a rotary movement of the astragalus. This accounts for the large percentage of oblique fractures (153 in 300 roentgenograms).

As before stated, Pott's fracture can occur with both supination or pronation of the foot at the time of accident. When pronation does not result after supination, there is a medial dislocation with a vertical or an oblique fracture in the tibia or in the internal malleolus.

A bimalleolar fracture is usually caused by supination or pronation but may be also caused by a fall forward or backward, with the foot either in plantar flexion or in dorsiflexion. The latter mechanism also accounts for a solitary anterior or posterior marginal fracture, in some of which we find a tear in the anterior or posterior tibiofibular ligament with diastasis.

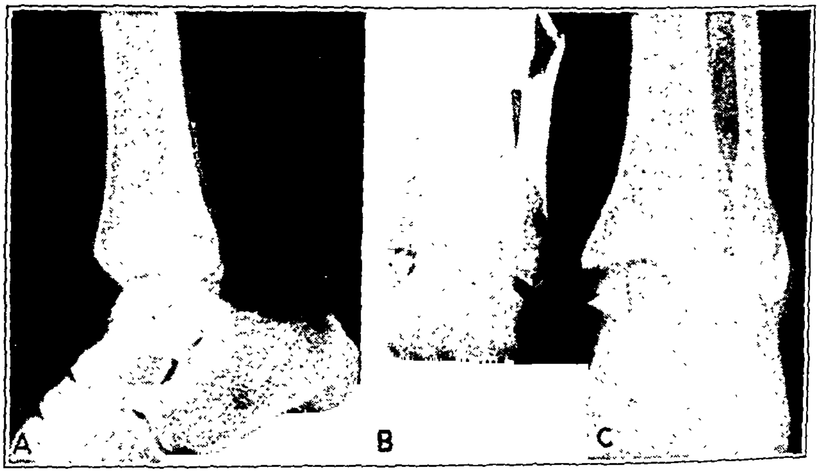

Fig. 9.—*A*, Pott's fracture with a posterior chip (a Tillaux fragment)—low oblique fracture of the fibula; *B*, Maisonneuve's type of Pott's fracture—a high fracture of the fibula, and *C*, simple Pott's fracture with fracture of the internal malleolus—low subperiosteal fracture in the external malleolus.

A marginal fracture usually occurs as a complication of pronation, supination or bimalleolar fracture. The posterior lip is more often involved because of its greater posterior declination. A posterior marginal fracture is more commonly seen in females than males, which leads us to believe that the equinus position of the foot allows greater rotation and backward displacement of the foot.

CLASSIFICATION

A study of 378 roentgenograms of fractured ankles makes us wonder why a classification should be made at all. It seems more natural to report each individual case according to the roentgenographic picture.

On the other hand, some classification which is simple must be used for teaching purposes. Our conception of these injuries does not permit a classification merely on the type of dislocation, since there are tears in the ligament and various combinations of fragments, nor can we consider one on an etiologic basis such as suggested in the excellent monograph by Ashhurst and Bromer.[5]

Regardless of any objection to placing a colleague's name in the classification, one must agree that for years English-speaking people have called the pronation fracture of the ankle joint Pott's fracture. There may be no Pott's fracture, but for the sake of precedent and usage from now on we shall classify all fractures of the lower part of the fibula with lateral dislocation of the foot as Pott's fracture; the reverse, as supination fracture. When there is no dislocation, one has simple or bimalleolar fracture. A compression fracture refers to upward dislocation of the astragalus with comminution of the lower end of the tibia and the fibula.

Should there be a small anterior or posterior lip (a Tillaux fragment) or an anterior or posterior marginal fragment (figs. 9 *B* and *C* and 10 *A*), this condition is considered as a complication. Solitary marginal fracture is rare. Thus we may refer to Pott's fracture with a posterior fragment or a bimalleolar fracture with an anterior Tillaux fragment.

This classification takes into consideration that lesions of the ankle consist of tears in the ligament, dislocations and fractures and quickly suggests to the student both the pathologic process and the treatment required.

TREATMENT OF INJURIES TO THE ANKLE

The main objects in treating injuries of the ankle joint are as follows: (1) to reduce the dislocation, (2) to reduce the fracture, (3) to reduce the tibiofibular diastasis, (4) to maintain a reduction until ligamentous and bony repair has been obtained, (5) to protect the vascular system during the repair and (6) to restore function.

As a temporary measure, in all cases of simple injuries of the ankle we apply a posterior molded splint lined with sheet wadding This is often done at home to protect the injury and make the trip to the x-ray laboratory or hospital more convenient to the patient. After the patient is hospitalized all compound fractures are surgically cleaned by débridement. No internal suturing is done, and the skin is closed without drainage. Fractures are immediately reduced, and a posterior molded splint is applied. If the wound is extensive and is so placed that the cast might produce pressure, the fracture-dislocation is treated by means of a Kirschner wire or a Steinmann pin through the os calcis, extension being best obtained with the knee bent on a Braun or Böhler splint.

It is important to ascertain whether the fracture-dislocation has occurred in the usual manner or whether there has been additional direct trauma, such as the limb's being run over by a car wheel, or any other form of contusion, since in such accidents the patient must be informed of the likelihood of blebs, gangrene or sloughs, lest he later blame the surgeon's splint.

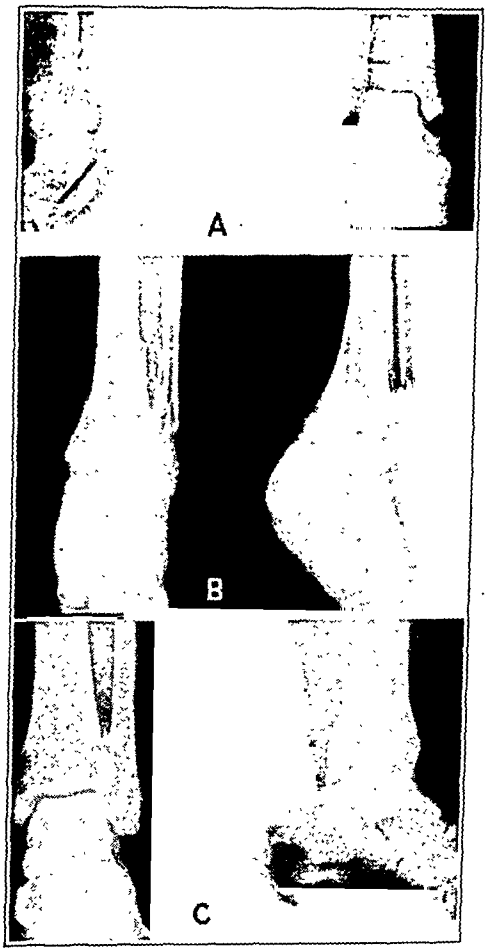

Fig. 10.—*A*, epiphysial separation with a posterior marginal fracture running into the epiphyseal line; *B*, supination fracture, and *C*, simple fracture of the external malleolus.

In simple fractures without dislocation or displacement an anesthetic may not be necessary since the limb can be immobilized with the usual posterior molded splint. If, however, there is considerable tenderness over the anterior inferior tibiofibular ligament or should the roentgenogram show a distinct diastasis, we even then use a local or general anesthetic in order to apply the redresseur.

Reduction.—This is done as soon as diagnosis is made by means of a roentgenogram. Should there be a swelling, the limb is elevated for twenty-four hours, and effleurage is used to reduce the edema.

The reduction should be done with the patient under an anesthetic, either local or general, preferably ether or ethylene. In all cases of Pott's fracture reduction is performed with the leg flexed at right angles, dorsiflexion and adduction of the heel being used, and for supination fracture-dislocations the reverse of this procedure is employed—with either type of fracture, the foot being held in midposition.

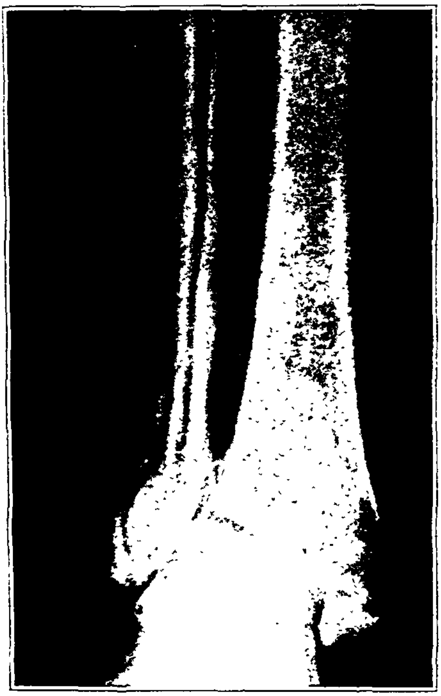

Fig. 11.—Pott's fracture with posterior marginal fracture, showing marked diastasis, suggesting also involvement of interosseous ligament.

All posterior dislocations with posterior marginal fragments are reduced with cautious dorsiflexion (see maintenance of reduction).

The internal malleolus, when fractured and displaced, is pushed upward with the palm of the hand.

Bimalleolar fracture is treated in midposition with right angle dorsiflexion.

It is the purpose of this paper to add one additional procedure in the reduction of Pott's fracture; that is to reduce the diastasis by means of a redresseur to the lower part of the tibia and fibula above the malleoli. The instrument is applied for from three to five minutes, the compression being removed just before the unpadded posterior molded splint of plaster is applied. Not alone is the diastasis overcome, but a better mortise and position of fragments are effected in a bimalleolar fracture. Neglect to reduce the diastasis results in abnormal lateral motion, pes valgus, shortening of the tendo Achillis, faulty weight bearing and later arthritic change.

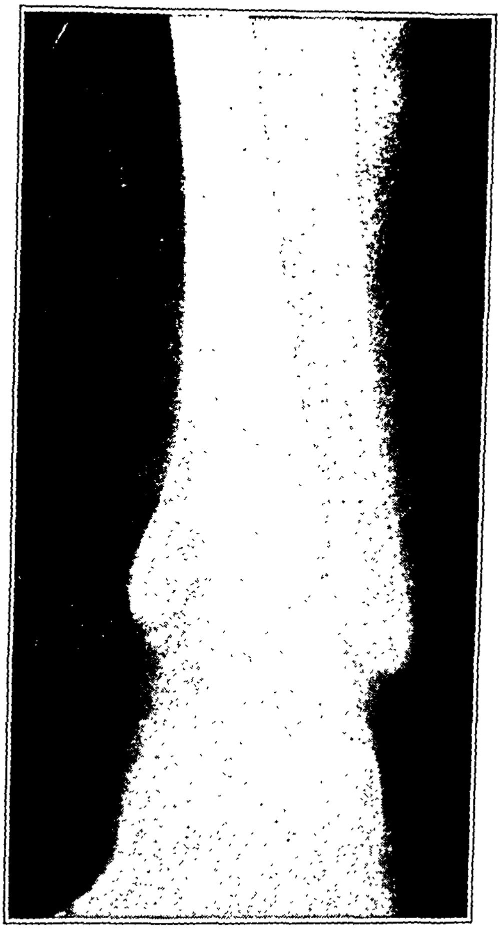

Fig. 12.—Simple Pott's fracture. The fibula is fractured at a still higher level.

When diastasis is marked and second roentgenograms still show separation, we apply extension by the Kirschner wire, which puts the collateral ligaments on stretch, thereby bringing the tibia and the fibula together. We here caution against overextension (fig. 14).

A common error is to put a supination fracture with medial dislocation in adduction. This only increases the dislocation.

When a posterior marginal fragment complicates fracture, caution should be used not to put the foot in too much dorsiflexion.

A compression fracture is treated as a routine with Kirschner wire through the os calcis. The reduction of dislocation can be obtained by adjusting the bow of the Kirschner apparatus. The redresseur is usually used later for this type of fracture because of the greater tendency to edema and blebs.

Maintenance of Reduction.—It is easy to reduce Pott's fracture even when complicated by a marginal fragment, but is is difficult to maintain the reduction, because the diastasis predisposes to redislocation of the astragalus. Formerly, many poor results could be attributed to the circular cast padded with so much cotton that the reductions were lost in the shrinkage of the plaster.

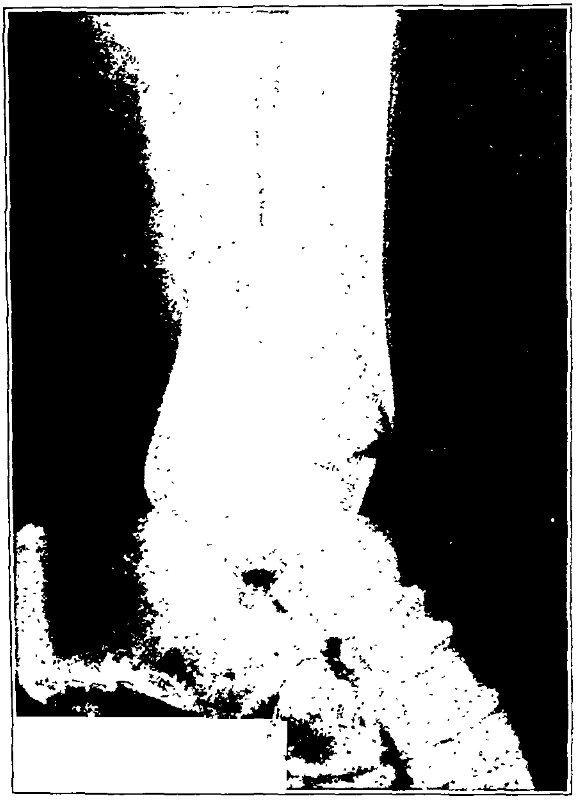

Fig. 13.—Pott's fracture with anterior and posterior marginal fractures.

The ordinary type of Pott's fracture can be best immobilized in a posterior molded splint without padding. This splint is applied immediately after the redresseur has been removed and extends from the middle of the thigh to beyond the toes. A walking iron can be applied several days later in cases of the more simple types of fracture by means of circular plaster above the malleolus and above the knee. Our statistics show that the average immobilization is about five weeks in a case of simple Pott's fracture and much longer when there is a posterior marginal fragment. In the latter cases one may not be able to maintain reduction in the ordinary plaster splint, and under such circumstances we advise using a pin or a Kirschner wire extension on a Böhler splint for five weeks. We advocate that extension be used more often in cases of the severe types of fractures of the ankle to reduce the diastasis, to prevent redislocation and to keep the posterior fragment pulled down.

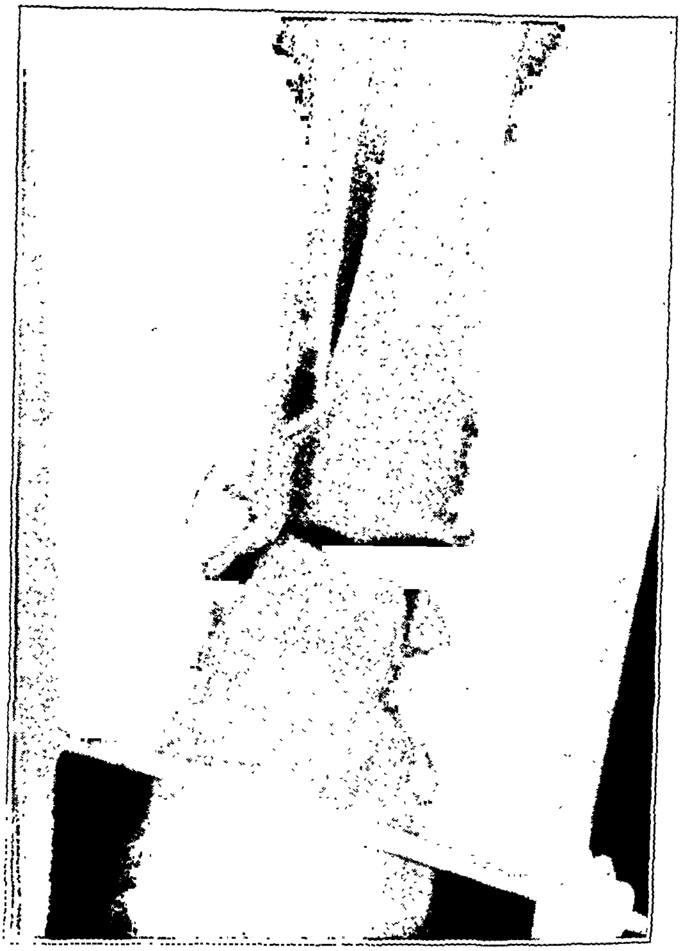

Fig. 14.—Overextension and deformity caused by improper traction.

Roentgenograms are made immediately after the reduction, and in cases of anterior or posterior marginal fragments they are made every seven days until union is assured.

In many cases a boot made of a paste of zinc oxide[29] is desirable during the next few weeks to support the circulation. Weight bearing varies with the amount of swelling and union. The average weight bearing in simple Pott's fracture is eight weeks. We advise against weight bearing in a case of Cotton fracture for a period of from twelve to fourteen weeks.

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[29] The composition of this zinc oxide paste by weight is as follows: 1 part of chemically pure zinc oxide, 2 parts of good gelatin, 3 parts of water and 4 parts of chemically pure glycerin.

Restoration of Function.—Passive motion is entirely omitted from our treatment. Active motion can be obtained even with a boot of a paste of zinc oxide. When the boot is not used, we find our best results in restoring function to be derived from the use of baking, Swedish massage and hot and cold foot baths.

The only additional treatment which we employ is the application of the redresseur in reducing tibiofibular diastasis, which is present in all injuries to the ankle, and to advocate a greater use of extension (traction) to prevent disabilities.

SUMMARY

In our report, supplemented by a morphologic and physiologic study and a clinical study of the pathologic picture of fractures of the ankle, we have emphasized the following points:

1. The primary lesion in leverage fractures of the ankle joint is the tear in the anterior inferior tibiofibial ligament, followed by a certain amount of diastasis.

2. The height of the fibular fracture depends on the degree of diastasis plus the gliding of the fibula in dorsiflexion and plantar flexion (already described).

3. The diastasis in the inferior tibiofibular articulation is the cause of much disability, faulty weight bearing and arthritic changes and should be prevented at the time of injury by applying a redresseur or even traction with a Kirschner wire at the time of reduction and immobilization.

4. All abduction fractures of the ankle joint should be called Pott's fracture. We have given a simple classification, including all other types of fracture and their complications.

RETROPERITONEAL TERATOMA

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AND
W. D. FRAZIER, M.D.
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The literature on the pathologic structure of the teratoma is in a most unsatisfactory state. On a recent occasion three pathologists were questioned as to the elements necessarily present in a tumor to admit it to classification as a teratoma. Each presented different criteria. The literature reveals a similar divergence of opinion, and the confusion is evidenced further by the number of theories that have been advanced by authors to explain the origin of such a tumor. To enter into a discussion of these subjects is beyond the scope of this paper, but the studies presented here strongly suggest that a teratoma arises as a misplaced blastomere. The more nearly totipotent the cell, the more differentiated will be the tumor when it grows.

Recognizing fully the objections to this theory, we believe that it still remains the most logical explanation of parasitic monsters and teratomas. By following this reasoning, teratomas may be subdivided into two types: the true teratoma and the teratoid tumor. The former, containing the analog of one or more organs, is derived from a more nearly totipotent blastomere than the latter, which is unable to produce any formed organ, even though it, too, contains representatives of all the embryonal elements. The transition between these artificial classes is so gradual that the classification accorded any borderline tumor depends on the pathologist. In reviewing the literature listed in the bibliography, we have attempted to ascertain from the description of the tumor whether or not formed organs were present, and our review has revealed thirty-six cases of retroperitoneal teratoma. The data in these cases, with the exception of those in the cases presented by Karvonen and Cahill, reports of which were not available, are recorded in the accompanying table. In addition we desire to present a new case which we have observed.

REPORT OF A CASE

P. S., a 29 year old man, was admitted to the surgical service of Dr. I. S. Ravdin in the Hospital of the University of Pennsylvania on Sept. 9, 1935, with a chief complaint of pain in the right side of the abdomen. He stated that his

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From the Surgical Clinic and the Laboratory of Surgical Pathology, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research.

Data on Cases of Retroperitoneal Teratoma and Teratoid Tumor Reported in the Literature up to 1936

Author	Sex	Age*	Location of Tumor	Size	Manner of Obtaining Specimen	Result of Operation	Formed Organs Present	Symptoms
Baljasov	F	21	....	..	Operation	Death	....	....
Bauer	M	14	Left	M	Operation	....	Yes	....
Brouha	F	26	Left	L	Operation	Death	No	....
Dickinson	F	2	Right	S	Autopsy	....	No	Mass
Durante and David	..	Neonatal	Lumbar	M	Autopsy	....	Yes	....
Feldmann	M	20	R. U. Q.	S	Autopsy	....	No†	Mass
Gordon	F	50	....	L	Operation	Recovery	No	"Pressure symptoms"
Gross	F	26	R. U. Q.	S	Operation	Recovery	Yes	Mass
Gude	F	9	L. U. Q.	M	Operation	Death	Yes	Mass
Hosmer	F	8 mo.	Right	L	Autopsy	....	Yes	Mass
Irna	F	9 mo.	Left	M	Operation	Death	....	....
Johnson and Lawrence	M	33 mo.	Left	S	Exploration	Death 8 mo. later	Yes	Mass
Kaneko	M	10 mo.	L. U. Q.	M	Autopsy	....	Yes	Mass; cachexia
Kolb	F	7 wk.	Left	S	Autopsy	....	Yes	Mass; cachexia
Kostitch	M	22	L. U. Q.	L	Operation	Death	Yes	Mass; pain
Kuznetsoff	M	..	Left	L	Exploration	Death	No	Mass; cachexia; constipation
Landivar and Iparraguirre	M	45	L. U. Q.	M	Operation	Recovery	Yes	Pain
Lexer	F	11	L. U. Q.	..	Operation (twice)	Recovery	No	Fever; pain; mass
Lightwood	..	9 wk.	R. U. Q.	S	Autopsy	....	No	....
Marchand	F	35	L. U. Q.	S	Operation	Death	No	Mass
Maydl	F	..	....	..	Operation	....	Yes	....
Meckel	..	..	L. U. Q.	..	Autopsy	....	No	....
Nicholson C. M.	M	25	R. U. Q.	S	Exploration	Death	Yes	Mass; vomiting; pain
Nicholson, G. W. P.	F	4 mo.	L. U. Q.	S	Autopsy	....	Yes	....
Pillet	F	21	Lower	L	Biopsy	Death	....	Mass
Portugal	F	17	L. U. Q.	S	Operation	Death	Yes	Mass; vomiting; pain
Roux	F	25	Umbilicus	L	Autopsy	....	No	Mass; uremia
Ruge	M	27	Left	L	Operation	....	Yes	....
Seki	M	22 mo.	Left	M	Autopsy	....	Yes	....
Shonholzer	M	2	Epigastrium	M	Autopsy	....	Yes	Mass; pain
Terasako	M	3 mo.	R. U. Q.	S	Operation	Death	No	Mass
Tillaux	F	22	L. U. Q.	M	Operation	Death	No	Rapid growth
Tsuda	M	17 mo.	Left	L	Operation	Death	....	....
Usandizaga and Mayor	F	28	L. L. Q.	S	Operation	Recovery	No	Pain
Watanabe	M	23	L. U. Q.	S	Autopsy	....	....	Mass

* Figures indicate years when not otherwise specified.

† Malignant.

health had been perfect until ten days before admission. Then, for the first time, he had noticed a dull pain in the right lower quadrant of the abdomen. This pain caused him to stop his regular work in a hosiery mill. A local physician examined him "thoroughly" and ordered him to bed. At no time did he have nausea, emesis or pyrexia. After two days of rest in bed the pain disappeared completely. On September 5, following the advice of his physician, the patient took a bottle of solution of magnesium citrate to relieve obstipation of six days' duration. This was effective, and after the passage there was noted for the first time a large nontender lump in the right upper quadrant of the abdomen. The mass persisted without change until his admission on September 9. Two days before, while walking, the patient was suddenly seized with knifelike pains in the right upper quadrant of the abdomen. These were excruciating for from five to six hours but after that gradually lessened in intensity until the time of his arrival at the hospital. Still there was no nausea, vomiting or fever.

His past medical history was essentially irrelevant, except that he had noted increasing constipation for the preceding two years. His family and social histories were not enlightening.

On physical examination, the patient was found to be well developed and to present no essential abnormality, save for the condition in his abdomen. In this region there was slight generalized tenderness, but no muscular spasm. In the right upper quadrant, nearer the umbilicus than the costal margin, a firm, smooth mass was felt, which on palpation seemed to be about the size of a lemon. It was well circumscribed and apparently did not extend toward the right costal margin. It was fixed, though it moved slightly with respiration, and was tender only to firm pressure. No other masses or organs were palpable.

Laboratory studies of significance showed a leukocyte count of 17,400 and a slightly accelerated sedimentation time. A roentgenogram taken after an enema of barium sulfate revealed the transverse colon displaced downward by a mass located in the right upper quadrant, which mass lay superior and posterior to the transverse colon but had no connection with it.

After two days' hospitalization a laparotomy was performed by Dr. I. S. Ravdin on September 11. Through an upper right rectus incision, the tumor was found to be lying retroperitoneally just below the liver, on top of the vena cava and lateral to the descending portion of the duodenum. Across its lateral surface ran the right ureter, and across the medial surface, the superior mesenteric vessels. It was covered by the transverse mesocolon, and when this had been divided the mass was found to be well encapsulated. The pseudocapsule or peritoneum was incised, and the tumor was carefully shelled out, with little bleeding. The posterior pole was firmly adherent to the vena cava. The raw surface was peritonized, and the abdomen was closed without drainage.

The patient's course after operation was uneventful. The incision was completely healed at the time of his discharge, on the sixteenth postoperative day. He returned two months later. At that time he felt entirely well, had gained weight and was completely relieved of his constipation. The wound was well healed and showed no evidence of weakness. No recurrent mass could be palpated. A series of high voltage roentgen treatments was given at that time. It was divided so that 50 roentgens was delivered through each of four portals covering the entire abdomen and the lower part of the thorax, and a second portion, consisting of 3,200 roentgens, was directed to the tumor bed.

Six months after his discharge the patient was readmitted to the hospital, because of a different complaint (headache). The opportunity was taken to study him at this time. Physical examination, a urogram and roentgen examination, after a barium enema, revealed no abnormalities in the retroperitoneal area. He had no symptoms referable to this region. The testicles were normal in size, shape and position.

He returned to the hospital in July 1936, with a painful swelling in the right side of his scrotum. This had developed rapidly, following an injury two weeks before. Examination revealed that the lesion was not traumatic or due to infection but was a neoplastic enlargement of the right testicle. The testicle was somewhat larger than a hen's egg and was firm, smooth and slightly tender and surrounded by a small amount of fluid. The patient's general condition was good, and he had lost no weight. General physical examination gave negative results. Orchidectomy was performed, and on microscopic examination typical teratomatous tissue was found, which we believe was the result of metastasis from his original tumor.

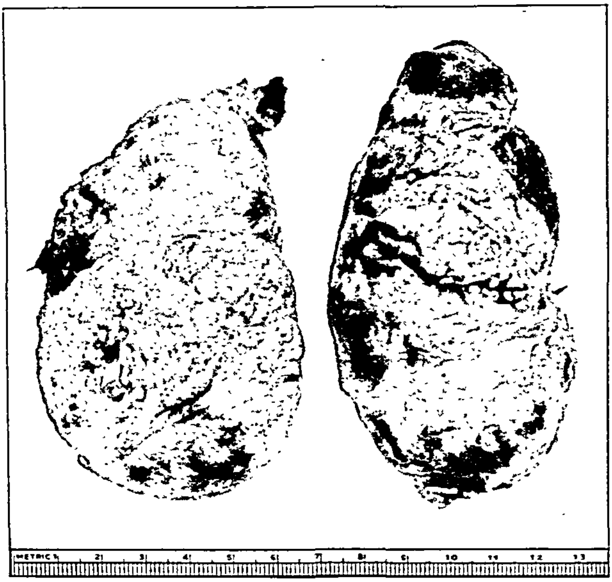

Fig. 1.—Outer view of the tumor, showing the nodular appearance. The site of attachment is at the top of the picture.

His fourth admission was only ten days later, and at this time he complained of a constant, dull, dragging pain in the right lower quadrant of the abdomen. There were no associated urinary or gastro-intestinal symptoms other than some increase in constipation.

Examination revealed a large firm, fixed mass just below the scar of the original operation and a smaller lesion farther down in the right lower quadrant. These had not been palpated at the time of the previous admission. Roentgen studies of chest, loins, spine and pelvis gave negative results, but the right iliopsoas muscle was partially obscured, apparently by the overlying tumor. These lesions seemed to be extensions of the original lesion. They were hard and fixed. We did not believe that they could be removed by operation. Roentgen therapy was begun immediately, and over a period of three weeks the patient received a total of 4,450 roentgens through six portals, covering the chest, abdomen and pelvis. During this time his pain was completely relieved, and the palpable masses decreased considerably in size. He was told to return for further irradiation after six weeks' rest.

Pathologic Report.—Grossly the tumor was the size and shape of a large pear. It measured 10 by 6 by 5 cm. and weighed 155 Gm. The surface was covered with a glistening capsule, save for an area 3 cm. in diameter, which was the apparent site of attachment. Its surface was irregular and nodular (fig. 1). These whitish yellow nodules measured from 1 mm. to 1.25 cm. in diameter. To palpation they felt firmer than the supporting tissues. On section the tumor was found to be made up of myriads of small cysts (fig. 2), the great majority of which were filled with a sebaceous material. There was a second group of apparently thinner-walled cysts which contained a clear serous fluid. A third, less common class was observed, which contained both clear serous fluid and sebaceous material.

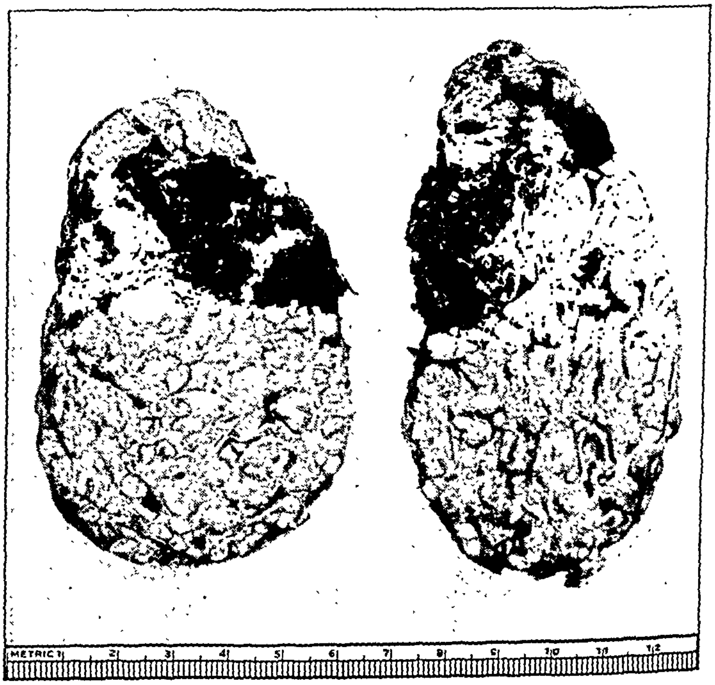

Fig. 2.—Inner view of the tumor, showing cystic structure. The areas of hemorrhage may be seen plainly.

The last two types of cyst were found, in the main, near the posterior attachment of the tumor. In the same area were several fairly well organized hemorrhages, the largest of which measured 3 by 3 by 1.5 cm. No formed organs were seen grossly.

Microscopically the tumor showed wide structural variations. Predominating were structures of mesoblastic origin. Among these, in order of frequency, were encountered spindle cells and connective tissue, moderate-sized, localized areas of angiomatous tissue, small areas of adipose tissue and one small plaque of cartilage. There was no evidence of the presence of muscle or bone.

Tissue of hypoblastic origin was least frequently seen. Several areas showed columnar epithelium bearing goblet cells. These were arranged in a manner resembling the glandular formation of the large intestine. The apparent secretion of these cells took the eosin stain. Occasional cysts were lined with epithelium of

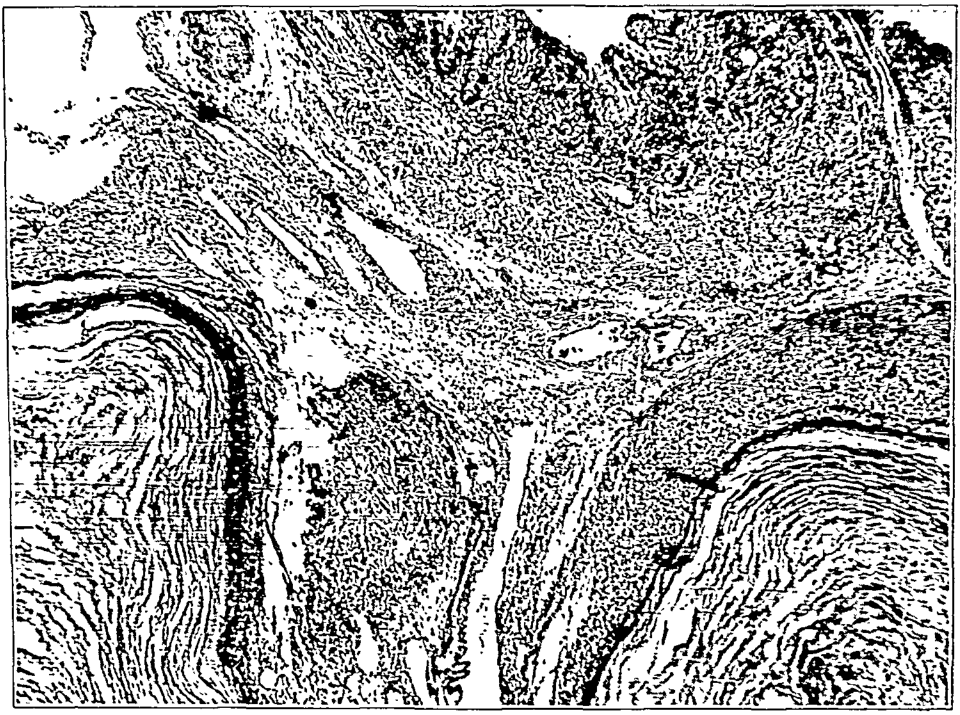

Fig. 3.—Photomicrograph showing three of the many cysts found in the tumor. The upper one is lined with goblet cells, and the lower two are lined with endothelial cells and filled with a colloid substance.

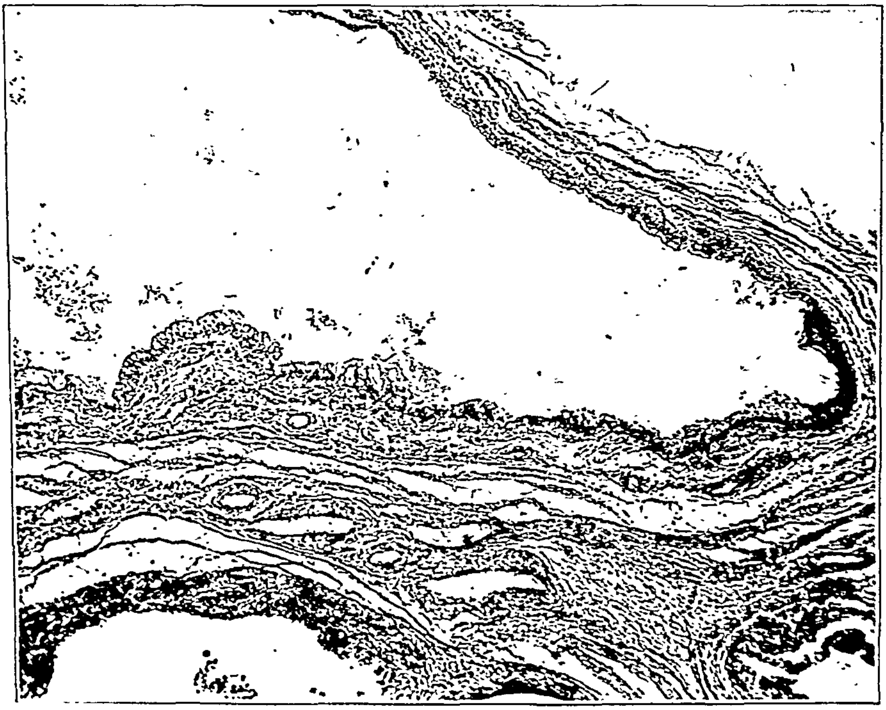

Fig. 4.—Photomicrograph showing a cyst lined with three different kinds of epithelium.

a pure columnar variety and others with a pure transitional type. In the latter class several papillary projections were observed. No cilia were demonstrated.

Epiblastic tissue was manifested by epidermoid cysts. These did not have hair, sweat glands or papillae, and it was impossible, therefore, to identify them as true skin. In one section there was observed what appeared to be a rudimentary hair follicle which contained no hair. By the use of silver stains, we discovered no evidence of neuro-epithelium.

There were some points of special interest in the microscopic examination: Several cysts were present which contained stratified, columnar and transitional epithelium (fig. 3). In some instances the cysts were empty. In others they contained what appeared to be desquamated epithelium. Still others had an eosin-stained secretion.

There were two hemorrhagic areas, one of which showed a more advanced degree of organization than the other. In the older of these great numbers of macrophages were observed to be carrying blood pigment. In the other the hemorrhage issued into a previously angiomatous region. There was some necrosis of the tissue adjacent to the hemorrhagic areas, and in these places were seen many old polymorphonuclear leukocytes, with a surrounding wall of lymphocytic infiltration.

There was no evidence of malignancy in any of the sections studied.

PATHOLOGIC STRUCTURE

The tumor under discussion contained elements representative of all the primary embryonal layers, but since it contained no formed organs it was necessary to classify it as a teratoid tumor. Both Lexer and Portugal stated that true teratomas are less common than teratoids. Kuznetsoff maintained that in the retroperitoneal area the opposite is true. An analysis of the cases presented here supports this view: Nearly two thirds of the growths were true teratomas. G. W. Nicholson has shown that several studies seem to report inaccurately the presence of formed organs. An epithelium-lined cyst containing an occasional goblet cell does not justify concluding that the tumor contains large intestine.

Structurally the tumor under study was not unusual. The great number and approximate equality in size of the cysts were noteworthy. Cysts containing three kinds of epithelium have been recorded by Lexer, Pilliet, Dickinson and others. The majority of tumors contain bone, but a roentgenogram of the tumor described here failed to reveal its presence. The area of cartilage was unusually small. No cholesterol crystals were detected by fresh smears.

The fact that one area of hemorrhage appeared to be further organized than the other gives rise to the thought that there may have been recurrent hemorrhages.

The size of the tumor under discussion was about the same as that of the growth in the case of Gross, which was the smallest previously recorded. That tumor also was located in the right upper quadrant, and the patient recovered after operation. Lexer stated that the majority of the tumors were located in the left upper quadrant, and, indeed, we were able to find only five previously reported that were located in the right upper quadrant.

CLINICAL SURVEY

A review of the cases studied shows some points of clinical interest. While there is no information available, it is probable that in few of the cases was a diagnosis made before operation or autopsy.

A tumor of this type is found usually before the patient reaches the age of 30. There were but three cases reported in persons past that age. Forty per cent of the patients were in the first decade, and 34 per cent, in the third. Distribution was nearly even between the sexes, fifteen being males and eighteen females.

An abdominal mass was the chief complaint in most instances. Pain was the next most frequent symptom, ranging in severity from a vague backache to the acute pain seen in the case here described and probably related to the hemorrhage found in the tumor bed. Vomiting and constipation were noted occasionally. These were due, in all probability, to external pressure. Fever was mentioned only once.

Rapid growth of the tumor was reported by Tillaux and was taken to indicate malignant change. Gradual loss of weight was the rule, and cachexia was seen in the terminal stages.

Physical examination invariably showed a tumor. The size ranged from that of a lemon to that of an adult head; the growth was usually located in the left upper quadrant, and generally was fixed. Edema of the extremities was recorded in several cases, and with a small tumor this might easily give a clue to the location of the lesion.

There are a few studies that might be of diagnostic value: A flat roentgenogram of the abdomen might reveal pieces of bone in the tumor. A roentgenogram taken after a barium enema would give valuable information as to the relative position of the tumor. One taken after the retroperitoneal injection of air, after the method suggested by Cahill, might aid further in localization. Urograms and pyelograms would help to rule out renal lesions, although they might show evidence of distortion due to external pressure. It is noteworthy that although such a tumor is in close juxtaposition to the kidneys, renal symptoms (except in the case reported by Roux) have been absent.

The chief differential diagnosis must be made from hypernephroma and retroperitoneal sarcoma. The more rapid evolution of the mass, the early onset of cachexia and the early metastasis point to the more malignant lesions. Often a hypernephroma gives rise to early renal symptoms and causes defects in the roentgenogram of the urinary tract. The presence of a febrile reaction is common in cases of sarcoma.

There are but two methods of treating these lesions. The first is surgical exploration and the removal of the tumor, either in whole or in part. In the cases here reviewed, twenty-three of the patients were operated on, of whom only seven survived—an operative mortality of 70 per cent. Of the seven who recovered, one died eight months later. Only a biopsy specimen had been removed from this patient at operation. In the remaining six patients the tumor was entirely extirpated, and as far as can be stated from the information available, there were no recurrences or further symptoms. Most of the deaths followed attempts at removal of a very large lesion. The cause of death in the majority of cases was hemorrhage and shock. Some of the patients might have been saved had modern methods of intravenous infusion and transfusion been available.

The other possible method of treating such a tumor is by interstitial irradiation. There is little information available on the subject, although it is well known that the tumor is highly radioresistant. The method might have definite application, however, in those instances in which the tumor appears to have undergone malignant degeneration. In a tumor which has been incompletely removed or from which a biopsy specimen has been taken, there is danger of seeding. From the malignant behavior of such seedings it must be deduced that they have taken in their growth a more anaplastic character than the cells from which they arose, in which case they should be more radiosensitive. We believe that all incompletely removed tumors and those from which biopsy specimens have been taken should have adequate roentgen therapy.

SUMMARY

The literature on retroperitoneal teratoma is reviewed.

A new case of retroperitoneal teratoid tumor is presented. The tumor was extirpated, and the patient was well six months after operation.

The diagnosis and treatment of lesions are discussed.

Dr. I. S. Ravdin granted us permission to discuss his case in this paper; Drs. A. E. Bothe and Charles C. Norris reviewed the slides, and Mr. Kitamura, a student at the university, supplied the translations of Japanese articles.

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TREATMENT OF COMPOUND FRACTURES

RESULTS IN ONE HUNDRED CASES OF COMPOUND FRACTURES OF THE TIBIA

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The result of any surgical procedure depends almost as much on the surgeon and his application of it as it does on the merits of the procedure itself. In no field is this more true than in the treatment of compound fractures. Here each fracture presents an individual problem, no two being exactly alike in any of the many particulars which affect the method and result of treatment. Even if one cannot or should not adopt a standard routine procedure for all fractures, it does seem that the treatment of so common and serious an injury should be more standardized than it is today. There is varied and conflicting counsel in textbooks and journals, and even in the large surgical services there is usually no standardized method of treatment. The results obtained by any of the various methods are not satisfactory. Cotton said: "Judging from what I see of end results, I fear that the problem of handling compound injuries needs constant attention and constant emphasis." In this situation it behooves every one periodically to review and critically and honestly evaluate the end-results of whatever method or methods he is using. I have tried to do this for the fractures treated in the first surgical division at the Bellevue Hospital during the past ten years. Because they are the most numerous and offer the most favorable opportunity for comparing different methods, this review has been limited to compound fractures of the tibia. During the past ten years 100 such fractures have been treated on which the records are complete as far as immediate results are concerned. Final results as determined by a follow-up study of more than one year were obtainable in 72 cases. These fractures were treated in a general surgical service by various methods by numerous surgeons and house officers. While this has many disadvantages, it does offer an opportunity to compare different methods.

The results have been bad. There have been numerous infections, several amputations and a few deaths. Part of this may be blamed fairly on the type of patient coming to a large city hospital. Many are addicted to the use of alcohol, many have eczema or ulceration of the legs and nearly all have dirty skin and clothing. However, most of the blame for the bad results must rest squarely on the surgeon. That these results are not peculiar to this service is evident from a study of the literature and by results seen elsewhere. Hey Groves said: "The results of treatment are extremely bad."

The chief problem in treating these injuries is the prevention of serious infection. There are many factors involved which do not lend themselves to statistical study. However, by analyzing a large number of cases of this type of fracture, one should be able to evaluate to some extent the importance of certain factors. In 23 of the cases at the Bellevue Hospital some degree of infection developed, varying from a mild subcutaneous cellulitis, or a persistent sinus, to violent sepsis.

The most important factor of all, as far as infection is concerned, is promptness of treatment. This is only partly under the control of the surgeon, but its importance should be strongly and repeatedly emphasized, so that there will be no unnecessary delay, such as results from transferring the patient from one hospital to another, etc. Of the patients entering the Bellevue Hospital more than two hours after the accident, infection developed in 50 per cent, whereas of those brought in less than two hours after the fracture occurred, infection developed in only 20 per cent. Admission to the hospital from one to two hours after the accident does not mean prompt treatment. Ideally the patient should be on the operating table within an hour after the accident. This factor is so important that I believe it is a mistake to lay too much stress on the treatment of shock and of the patient's general condition, as is done in most textbooks and medical schools. Débridement, reduction and immobilization of a fracture need not be shocking procedures and can well be carried out coincidentally with the treatment of shock. In fact, I think that it is a part of this treatment. Certainly a patient will recover from shock more readily with the fracture reduced and securely immobilized than he will in uncomfortable, inefficient temporary splints. The time element is so important that débridement should be carried out without delay while the patient is receiving infusion or transfusion and other measures to combat shock.

Every one agrees that débridement and mechanical cleansing of the large wounds communicating with a fracture should be done when the patient is received reasonably early. However, there is a difference of opinion as to whether anything is gained by débridement of the small puncture wounds made from within outward by spicules of bone or by the sharp edges of larger fragments. These wounds are small and innocent looking, the fragments have slipped back into more or less good position, and it is a temptation to apply a little iodine, cover the wound and treat the injury as a simple fracture. Estes advocates this simple course, and as evidence that others besides my co-workers and me do not always practice what they preach, Leland reported débridement of only 12 of 22 wounds. However, the size of the wound bears little relation to the damage to the parts beneath, and bits of dirt or clothing may have been pulled into even a small opening. Therefore, we believe there should be no compromise. Débridement and mechanical cleansing should be done of all wounds communicating with a fracture, no matter how small. Cotton, Foster, Speed and Wilson agree with this. We had 27 cases of fracture which were seen early in which the wound was less than ½ inch (1.3 cm.) in length. Débridement was done in 7, and infection developed in only 1; débridement was not done in 20 cases, and infection developed in 5. Thus the incidence of infection was cut almost in half by débridement. It is reasonable to suppose that the smaller and cleaner wounds were the ones not subjected to débridement, making the decrease in the rate of infection even more striking.

Many writers speak of the danger of further contamination of the wound while scrubbing, owing to soap and dirt being carried into the wound. Some advise covering the wound and not attempting to scrub the edges. Leaving the most important part of the operative field untouched seems entirely illogical to us, and we believe that the danger can be obviated by scrubbing the wound under a constant stream of water. The direction of flow is always away from the wound, and there is but little chance of carrying dirt into it. The process should be just as thorough and conscientious as the cleaning of the surgeon's hands. Asepsis is only as strong as the weakest link in the chain, and it is most unreasonable to spend eight or ten minutes by the clock scrubbing and disinfecting the hands, covering them with rubber gloves and then operating in a field that has been carelessly cleaned and painted with some confidence-inspiring antiseptic. The operative field should be scrubbed for at least ten minutes under a constant stream of water, cleaned with alcohol and ether and then painted thoroughly with iodine or some other antiseptic. The edges of the skin and all devitalized tissue should be excised and the wound again irrigated.

After cleansing and débridement, the question arises whether to close the wound, drain it, pack it open or start immediate treatment with a diluted solution of sodium hypochlorite. Cotton, Estes and Stimson advise loose suture of the cleaner wounds, without drainage. Wilson and Cochrane advise suture only in the cases in which treatment is given within twelve hours after injury and in which the surgeon feels absolutely certain that mechanical sterilization has been obtained. Gurd uses the bismuth-iodoform paste treatment popularized during the World War. This is essentially the same as the Orr treatment, as the mild antiseptic value of the bismuth-iodoform paste is of no importance. Foster leaves the wound open and treats immediately with a diluted solution of sodium hypochlorite. Of the cases of fracture at the Bellevue Hospital in which the patient was treated soon after injury, débridement and suture without drainage were done in 34; of these, infection developed in 7, 21 per cent. Twenty-five wounds were left open without drains or packing; of these, 5, or 20 per cent, became infected. Of the

12 packed open, infection developed in 2, or 17 per cent. Thus it is seen that statistically there is little difference between suturing, packing and leaving the wound open. Except for the fractures seen soon after the accident, packing is the safest treatment. Little is lost by packing as the wound heals by granulation before bony union occurs. One important fact is brought out by the 7 cases in which suture and drainage were done; the wound in 3, or 43 per cent, became infected—more than double the incidence by any other method. The rubber tissue drain inserted "because there is oozing" or "to allow the escape of serum" is not only useless but definitely harmful. It acts as a foreign body, increasing the exudation and preventing the tissues from exerting their strong defensive mechanism. All these wounds are contaminated, but if the tissues are given a chance they will overcome what organisms remain after débridement. This is becoming universally recognized as regards the peritoneum, joints and blood stream, and we believe that it holds true of bone and muscle. There should be no compromise, no middle ground. Either the wound should be closed, or it should be left open and packed lightly with gauze treated with petrolatum.

All of our patients were treated either by traction or with plaster splints or casing. Statistically, there is little difference in the incidence of infection, 30 per cent of those treated by traction and 24 per cent of those treated in plaster becoming infected. We believe that when the fragments can be held in good position in plaster, the secure immobilization is a great advantage in decreasing the incidence of infection and delayed union. Three of the 21 patients treated by traction had delayed union, whereas only 1 of the 63 treated in plaster failed to get bony union within six months.

Numerous surgeons have had the temerity to apply internal fixation to these open, potentially infected wounds. According to Wilson and Cochrane, the method has been superseded and should be used only in rare and exceptional cases. Hey Groves is more vehement. He stated: "I say quite deliberately that I regard the plating of an open fracture as a surgical crime." In the face of this, Foster reported results in a large series of fractures from Sherman's clinic which no one else has approached. Of 304 fractures, he plated 146 and not only had no severe infections but had fewer persistent sinuses in the cases in which plating was used than in those in which it was not employed. Recently we plated a few compound fractures with good results, but we believe that the method should be reserved for the exceptional fracture, i. e., the fracture seen soon after injury in which mechanical cleaning is satisfactory and in which reduction cannot be retained by other methods.

We were forced to amputate in 5 cases. In 2 of these primary amputation was done because of nonviability of the foot. One man refused operation on admission to the hospital, and infection developed, necessitating amputation. In a boy of 12 years with extensive avulsion of the skin and soft parts by a crushing injury, a severe infection developed, and the leg was amputated on the fourth day. Another fracture involving the ankle joint was manipulated in the presence of active infection, which is extremely poor surgical judgment, and a violent flare-up of the infection occurred, necessitating amputation.

In this series of 100 cases there were 8 deaths. Five were due to associated injuries and 1 to pneumonia three weeks after the fracture, so that only 2 deaths may be directly attributed to the injury. In 1 of the fatal cases the wound was closed loosely without drainage, and the fracture was immobilized in plaster splints. In the other débridement and loose suturing were done after the insertion of two soft rubber drains. A posterior molded splint was applied. The wound was infected, and amputation on the seventh day did not save the patient's life. The two surgical errors in this case—partly closing and draining the wound and poor immobilization—undoubtedly contributed to the fatal outcome. A posterior molded plaster splint is an absolutely useless gesture toward immobilization, yet for some queer psychologic reason it is one of the most frequent methods of splinting. The splint always breaks at the knee and ankle because a flat strip of plaster has practically no resistance to bending in the direction of its flat surface; also it is applied over the irregular thick soft parts of the calf rather than over the medial surface where the bone is superficial. In minor fractures, where one strip of plaster is to be relied on it should be applied on the lateral or medial surface, and the lower end passed under the instep and over the dorsum of the foot. Applied in this way it at least has some effect.

CONCLUSIONS

I have nothing new or startling to report in the treatment of these fractures, but a fairly large series of fractures is reported in order to emphasize the seriousness of this injury and the great room for improvement in results obtained here and elsewhere. The mortality, loss of function, period of hospitalization and economic loss are greater than for surgical diseases which receive much more attention and thought.

After reviewing the subject I feel more strongly than ever that this type of fracture presents an urgent surgical emergency. Débridement and thorough cleansing of all wounds that communicate with a fracture should be done no matter how small or clean they seem. The apparently clean wounds that are seen soon after injury in which mechanical cleansing is adequate should be sutured without drainage. Where treatment has been delayed or is not adequate for any reason, the wound should be left wide open and packed lightly with gauze treated with petrolatum. Immobilization in a plaster is superior to traction suspension in that it lowers both the incidence of infection and the incidence of delayed union or nonunion.

A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 210)

BLADDER

Physiology.—Rubritius[52] stated that the hollow muscular organs behave according to the laws which govern all the nonstriated muscles. The peristalsis of the hollow tubiform organs as well as the phases of filling and evacuating of hollow spherical organs can be explained by these principles.

During the phase of retention the wall of the bladder expands by the accumulation of urine, while its resistance remains the same. During this phase the internal pressure of the abdominal cavity is transmitted only partially to the internal pressure of the bladder on account of the tonus, that is, the resistance of the wall of the bladder. The capacity of the bladder is dependent on the tonus of the moment. When the maximal capacity has been reached, the contractive stimulus passes into the most extended muscular zone, that is, into the detrusor muscle.

With the contraction of the detrusor muscle, the sphincter relaxes. The tonus of the sphincter and the tonus of the detrusor muscle are dependent on each other; therefore, the sphincter remains open until the detrusor muscle has contracted completely, while the closing contraction of the sphincter puts an end to the contraction of the detrusor muscle. If the tonus of the sphincter is abnormally high, the closing contraction begins prematurely, and residual urine remains in the bladder. The presence of residual urine has a compensatory effect, because a bladder holding residual urine can work more economically and stand a higher pressure, so that it may keep up its function in spite of the obstacle to the outflow of urine.

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[52] Rubritius, Hans: Die Physiologie der ableitenden Harnwege, Kong. d. internat. Gesellsch. f. Urol. **6**:499-574 (Sept.) 1936.

While the bladder is contracting (transporting phase of the bladder), the peristalsis of the upper portion of the urinary tract ceases. The pelvis of the kidney and the ureter remain in a state of tonic extension (phase of retention). In the meantime the orifices of the ureters do not open, and urine flows out of the collecting tubes into the calices and into the pelvis of the kidney. The alternation of the phases of the bladder with those of the upper part of the urinary tract is regulated by reflexes. Any disturbance causes a vesico-ureteral reflux or upward flow.

Recent research has demonstrated that the resorptive efficiency of the mucous membrane of the urinary passages increases with the increasing dilatation of the mucous membrane. Gruber has confirmed the statements of former research workers that a close relation exists between the capillaries and the epithelium of the mucous membranes. This is especially true within the fornix calicis. It is known that the fornix calicis is the most extensible part of the urinary tract. Macroscopic rupture of the mucous membrane of the fornix calicis is of great importance in urinary retention, but there is no reason to look on this rupture as a physiologic phenomenon. If the mucous membrane in the fornix stretches to such an extent that there is utmost thinning of the epithelial cells although rupture has not yet occurred, this mucous membrane becomes permeable.

Urinary passages are, from a physiologic point of view, a closed system, the single morphologic units of which are working hand in hand. The connection of this system with its headquarters, the parenchyma of the kidney, seems to be very ingenious and enables undisturbed cooperation between them. In the urinary passages muscular action is completed by resorptive action. While the physiologic analysis of the former can be considered ideal, new questions are arising with regard to resorptive functions. Their importance from the standpoint of metabolism, the entire body and the connection with the minute collecting system of the kidney with the secretion of this organ are no doubt of great importance for future research.

Calculus.—Hueck[53] in ten years performed 171 operations for stone in the bladder. A previous operation had been performed to remove calculi in 14 of these cases, and in 1 case 2 previous operations had been performed. A single stone is usually found, as was the case at 50 operations on 44 patients. The average interval between surgical intervention and reformation of the stone was four years and eight months; in 1 instance it was less than a year. Because of the frequent adhesions between the peritoneum and the bladder, the author advised operation by the perineal route for recurrent calculus with the patient under sacral anesthesia. Thirteen of the patients were men, and 1 was a woman who had a vesicovaginal fistula. In 3 other cases of stone in women, vaginal fistulas were also present. This led the author to think of catarrh of the bladder as a predisposing factor of formation of calculi.

Of the 171 operations, only 10 were performed on females, whose ages ranged from 7 to 75 years. In Professor Olpp's series of cases of vesical calculi from the same hospital, 4 of the patients were women and 201 were men. Twenty of the author's patients were boys. In a series of 100 recent cases, 9 patients died within one month after the operation. This figure included elderly persons and those in whom complications developed. He had another series of 45 operations without a death.

In the author's opinion there has been no decrease in the number of cases of vesical calculus in recent years. Regarding the cause, he thought that hypothetically the body constitution, the composition of water and vitamin deficiency may play a rôle; ankylostomiasis, malaria and the dysenteries are listed among the predisposing causes. In this connection, Hueck commented on the rarity of cases of stones in Europe at present compared with their frequency in the Middle Ages.

Digby[54] stated that litholapaxy takes much time and patience. The actual procedure for stones over 1 inch (2.5 cm.) in diameter may consume from three quarters of an hour to a couple of hours. This compares unfavorably with the twenty minutes or less required for suprapubic cystostomy, but the extra time involved is well repaid by the benefits to the patient. Open warmed ether administered by a pump is the routine anesthetic. The table is slightly tilted so that the head is lower, and there has not been any difficulty with bronchitis in this class of case. From a theoretical point of view, sacral anesthesia should be ideal, as it should produce anesthesia of the bladder and urethra and relaxation of the detrusor fibers. It has been tried in a few cases and has worked out badly. Contrary to physiologic theory, the bladder seems to contract around the stone and interfere with manipulations. Spinal anesthesia is mentioned only to be condemned, at any rate, for the neglected patient with a large stone of long standing and possibly damaged kidneys. Such cases form the bulk of the cases of vesical calculus. Spinal anesthesia lowers the blood pressure, and anuria may follow. Digby stated that he had encountered this condition more than once when he had been called to see a patient in consultation after operation by others. Spinal anesthesia has not been employed for removal of a vesical calculus in his clinic.

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[53] Hueck, O.: Beitrag zur Blasensteinerkrankung, Chinese M. J. **50**:833-836 (June) 1936.

[54] Digby, K. H.: Observations on Litholapaxy, Chinese M. J. **50**:837-845 (June) 1936.

Litholapaxy is contraindicated in the following circumstances: 1. When there are signs of renal failure, such as suppression or extreme diminution in excretion of urine or a glazed and dry tongue, or the value for blood urea is more than 50 mg. per hundred cubic centimeters. 2. When the prostate gland is felt to be much enlarged on rectal examination or has been producing symptoms. In this case a suprapubic cystostomy with extraction of calculi should be followed in a week by suprapubic enucleation of the prostate. In these cases there are usually multiple calculi. More than one stone in an old man should always raise the suspicion of enlargement of the prostate gland, as should also the discovery of residual urine. 3. When there is a stricture of the urethra of any marked degree. Although the stricture can be dilated and the litholapaxy proceeded with, the more prudent method is to accompany the dilation with suprapubic cystostomy, unless the stricture is slight. 4. When the stone has caused a penetrating ulcer of the wall of the bladder so that extraperitoneal extravasation of urine has occurred, or a vesicosuprapubic fistula or a vesicorectal fistula has formed. 5. When advanced cystitis is present to such a degree that the urine is foul smelling, brown and ammoniacal and the bladder cannot be distended with fluid. In such cases suprapubic cystostomy is wiser. 6. When the stone is large. This is usually but not always a contraindication for litholapaxy. Very large stones have been crushed by experienced surgeons.

A surgeon should always be prepared to deal with any possible accidents. The posterior part of the urethra or the neck of the bladder may be perforated in passing one of the instruments. The wall of the bladder may be nipped and crushed. Severe crushing of the wall can be avoided by rotating the blades in the initial position before crushing the stone. The blade of the lithotrite used for the male may break or, worse, may bend. In the first case the lithotrite can be withdrawn without the blade. The broken blade has to be removed suprapubically. In the second case, after the bladder has been opened suprapubically, the blades should be protruded as far as possible and an attempt made to detach the bent blade with a hack saw. If the blades cannot be protruded far enough, the staff must be sawed through with a hack saw and the bent distal part of the lithotrite extracted through the suprapubic wound. The blades may jam on a cystine calculus. A fragment of stone may be overlooked at litholapaxy and become impacted in the urethra before the subsequent cystoscopy.

Kya [55] reported the results of a chemical analysis of vesical calculi in 42 cases. In 16 cases (38.4 per cent of cases analyzed) the stones contained uric acid as the chief constituent; in 18 cases (43.2 per cent of cases analyzed) there were mixed stones containing uric acid, calcium oxalate and calcium phosphate in balanced proportions. He stated that mixed stones are the commonest variety, and next to them are the uric acid stones. Rarely are pure stones of one constituent only found. The result of analysis of this series agrees with the figures of Jones in England, of Newcomb in India and of Thomson in Canton in that stones containing uric acid and urates as the chief constituent form a higher percentage than other stones.

Oxalate stones are seen in children, while uric acid or urate stones are obtained from middle aged or elderly patients.

The visibility of vesical stones of different chemical composition in roentgenograms has been dealt with. Kya had only 1 pure uric acid stone which was translucent to the roentgen rays. All other uric acid stones showed well in the roentgenograms, because they contained a certain proportion of calcium. Pure cystine is invisible in body tissue to detection by roentgenographic examination, but the stone which was 96 per cent cystine, 0.8 per cent calcium and 0.6 per cent phosphate showed distinctly in the roentgenogram. The opacity was probably due to the contained calcium.

Lett [56] stated that during the thirty year period previous to 1934 there were 2,781 patients with stone in the urinary tract admitted to the London Hospital. A study of this series suggests that stone in the urinary tract as a whole is twice as common in the male as in the female. The sex of the patients with stone in the kidney was fairly evenly distributed, as 849 of the patients were males and 719 were females. Of those with stone in the ureter, 353 were males and 179 were females, so that the former outnumbered the latter in the proportion of 2:1. However, when the patients with stone in the bladder were considered, there was a very great preponderance of males, as only 8.2 per cent of the patients were females.

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[55] Kya, L. T.: The Composition of Vesical Calculi, Chinese M. J. **50**:797-806 (June) 1936.

[56] Lett, Hugh: On Urinary Calculus, with Special Reference to Stone in the Bladder, Brit. J. Urol. **8**:205-232 (Sept.) 1936.

During the last ten years of the period under review there was a considerable increase in the number of patients with urinary stone admitted to the London Hospital, for, including those with stones impacted in the urethra, they numbered 1,085 as against a total of 778 admitted from 1915 to 1924, an increase of nearly 50 per cent. The number with renal calculi rose from 485 to 644; with ureteral calculi, from 130 to 208, and with vesical calculi, from 140 to 212. However, the number of patients with urethral calculi decreased from 23 to 21. Instead of an increase in the number of children with stone, the incidence fell from 69 during the period from 1905 to 1914, to 27 during the last ten years, largely owing to a diminution in the number of patients with stone in the bladder and urethra. It is interesting to find a definite increase during the five years that followed the World War, particularly in the number of patients with stone in the kidney.

Stones were found in the kidney in 1,568 patients, in the ureter in 532 and in the bladder in 608. The total of 2,781 patients in the series is completed by 73 with stone in the urethra. Thus there was a combined total of 2,100 persons with stone in the kidney and ureter as compared with 608 with stone in the bladder.

The urine of 750 consecutive patients with stone in the urinary tract was examined. This group was made up of 487 with stone in the kidney, 140 with stone in the ureter and 123 with stone in the bladder. The reaction of the urine was acid in 72 per cent of all instances in which it was examined. No report was made on the reaction of the urine of 4 of the patients with renal calculus, but that of 347 was acid, that of 41 was neutral and that of 95 was alkaline. Repeated examinations of the urine of a number of patients were made; the reaction of specimens of 103 varied on different occasions, while the first specimen of 67 was acid. Reports were made on the urine of 139 patients with calculus in the ureter; that of 102 gave an acid reaction, that of 10 was neutral and that of 27 was alkaline. Repeated examination of the urine of 29 patients disclosed varying reactions, while the first specimen of 24 was acid. The urine of 88 of the 123 patients with vesical calculus was acid, that of 10 was neutral and that of 25 was alkaline. There were 25 patients whose urine gave different reactions on repeated examinations, and 22 whose first specimen was acid.

Tumor.—Gehrmann[57] stated that prolonged exposure to relatively low concentrations of certain intermediates produced during the manufacture of dyes and classified as aromatic amines is known to have caused the development of tumors of the bladder in certain persons. The carcinogenic compounds already mentioned enter the circulation through three routes: (1) respiratory, (2) cutaneous and (3) gastro-intestinal. It is generally agreed that the most important route of entrance is through the respiratory tract, in the form of dust and fumes. Absorption through the gastro-intestinal tract is probably of the least importance. However, it must be remembered that present knowledge indicates a long period of exposure to low concentrations as an etiologic factor. Therefore, any absorption through the gastro-intestinal tract should be considered as of more or less importance, despite the low solubility of these compounds.

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[57] Gehrmann, G. H.: Papilloma and Carcinoma of the Bladder in Dye Workers, J. A. M. A. **107**:1436-1438 (Oct. 31) 1936.

The classic symptoms of tumor of the urinary bladder are hematuria, frequency, urgency, burning and pain. These symptoms as a group occur in Gehrmann's experience only in those cases in which the condition is well advanced. It has also been his experience that cystoscopic examination is the only safe method of early diagnosis. The growths may be single or multiple, papillary or sessile, infiltrating or noninfiltrating, ulcerating or nonulcerating, malignant or benign. In Gehrmann's group of 63 cases of tumor of the urinary bladder, 38 were carcinomas.

The histologic structure of the aniline tumor does not differ from that of tumors of unknown etiology. The aniline tumor occurs in all gradations, from the slowly growing villous papilloma, which may remain latent for many years, to the rapidly growing destructive and anaplastic carcinoma, which produces early and widespread metastasis.

Preventive measures are divided into two groups: plant operative control and medical control. The plant operative measures consist of manufacturing processes that provide complete protection against any exposure to dust or fumes. Every applicant for work in regions in which he will be exposed to aniline, alpha and beta naphthylamine and benzidine should have a cystoscopic examination in addition to a regular complete physical examination. Any disease of the genito-urinary system is a contraindication to employment, as is a family history of cancer and a history of hematuria or venereal disease. No applicant for this type of work should be accepted who is less than 21 or more than 40 years of age. All workers should have a complete physical examination and cystoscopic examination once a year. Every three months there should be a complete urinalysis and, on the appearance of macroscopic or microscopic blood, cystoscopic examination is indicated.

The prognosis is good in cases of benign tumor. However, further growths may occur at any time and may be primarily benign or malignant. The prognosis in cases of malignant aniline tumor of the bladder in general is not favorable. Simon expressed the belief that this type of growth is biologically different, runs a slower course and responds better to therapeutic procedures.

Dart[58] reported a study of the cell types and the methods of grading of the cases in the Carcinoma Registry of the American Urological Association. Since the opening of the registry in May 1927, more than 1,400 cases have been reviewed. Follow-up reports have been obtained each year on all but 77 cases. One thousand, two hundred and twenty-four of the 1,400 cases were used as the basis of this report.

With few modifications, the present criteria for grading tumors of the bladder used in the registry office are the same as those adopted by the original registry committee in 1927. These criteria are based on a combination of clinical factors and the histopathologic appearance of the specimen. For the purpose of these studies this has been designated as the registry grade. As a check on the efficiency of the registry grade, the registrar chose other criteria based solely on the histopathologic appearance of the tumor. This is referred to as the histologic grade. The underlying principles used in establishing the histologic grade are much the same as those which have been followed more or less consistently by all workers since Broders first announced his method.

The final grade and status of the 1,224 epithelial tumors of the urinary bladder were as follows: The registry grading (clinical data and cellular character) revealed 46 papillomas and 65 carcinomas of grade 1, 347 carcinomas of grade 2, 584 carcinomas of grade 3 and 182 carcinomas of grade 4, making a total of 1,224. The histologic grading (cellular character) revealed 101 papillomas and 200 carcinomas of grade 1, 266 carcinomas of grade 2, 459 carcinomas of grade 3 and 198 carcinomas of grade 4, making a total of 1,224.

Based on all of the facts found, it is believed that the present registry grade may be simplified, to advantage, as follows:

Grade 1. Papillary carcinoma. This type includes all papillary tumors in which there is no clinical evidence of infiltration and in which no obvious infiltration of the pedicle or the wall of the bladder can be demonstrated on histopathologic examination, and most of the cells are typical in appearance and arrangement.

Grade 2. (*a*) Papillary and infiltrating carcinoma. Obviously this type includes infiltrating papillary tumors and carcinomas in which the papillary structure is recognizable but most of the cells are atypical in appearance and arrangement. (*b*) Infiltrating carcinoma. This type includes the nonpapillary squamous cell carcinomas in which the cells are fairly uniform in size and type or have a tendency to form keratohyalin and epithelial pearls.

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[58] Dart, R. O.: Grading of Epithelial Tumors of the Urinary Bladder: A Study of the Cell Types and the Methods of Grading of the Cases in the Carcinoma Registry of the American Urological Association, *J. Urol.* **36**:651-668 (Dec.) 1936.

Grade 3. Nonpapillary infiltrating carcinoma. This classification refers to the very anaplastic infiltrating carcinomas. Practically all of the cells are atypical in appearance, and there is very slight or no differentiation.

Although definite conclusions cannot be made concerning the efficiency of grading of vesical tumors until more growths have been checked for a longer period, these studies indicate that it is impracticable to attempt the segregation of tumors of the bladder into definite groups corresponding to their cell types. For all practical purposes, epithelial tumors of the bladder may be classified as papillary, papillary and infiltrating, and infiltrating. Carcinoma of the bladder cannot be graded on the basis of cell differentiation alone. The mortality for the more differentiated types, such as acanthoma, is practically the same as that for the less differentiated squamous cell tumors. The most practical method of grading is based on a combination of physical and histopathologic observations.

Colston and Leadbetter [59] studied 98 cases of extensively infiltrating tumor of the bladder in which necropsy was performed at the Johns Hopkins Hospital; they attempted to correlate the history, methods of treatment and postmortem observations. The growths were exclusively epithelial tumors, with the exception of 1 sarcoma. Metastasis occurred in 56.1 per cent, and in 10 cases the tumor extended through the wall of the bladder without producing metastasis. Tables are given on each grouping and on the duration of symptoms compared with metastasis and extension, organs involved by metastasis, the pathway of metastasis, the comparison of treatment with occurrence of metastasis and the cause of death in operative cases. The importance of ureteral obstruction with resulting infection and destruction of renal tissue either from direct invasion of the tumor or from sclerosis of the ureteral wall due to scar tissue has been emphasized. A particular study of the microscopic structure of the tumors was undertaken to determine if they could be classed according to the cellular structure and architecture of the tumor as a whole. A tentative classification has been made, consisting in order of frequency of occurrence of (1) papillary carcinoma, (2) transitional cell carcinoma, (3) squamous carcinoma and (4) undifferentiated carcinoma. All of the tumors studied, with the exception of a few in the papillary group, were graded 3 or 4 according to Broders' classification. The papillary carcinomas revealed the smallest incidence of metastasis and the undifferentiated carcinomas the greatest, with the incidence in the squamous and epithelial groups lying between. The undifferentiated group is characterized by extensive and rapid metastasis. The squamous epithelial tumors had a tendency to extend first to the regional lymph nodes, perhaps later involving the liver, lungs or bones, while the other two types of tumors in many instances showed distant metastasis without involvement of the lymph nodes.

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[59] Colston, J. A. C., and Leadbetter, W. F.: Infiltrating Carcinoma of the Bladder, J. Urol. **36**:669-689 (Dec.) 1936.

As in all series of cases, various types of treatment had been used. It was impossible to state definitely the effects of treatment in the various groups, but the author's impression was that the undifferentiated type and the papillary type responded best to radium and high voltage roentgen therapy, as evidenced by the degree of destruction of the original tumor. The local response of these exceedingly malignant tumors to radium and high voltage roentgen therapy, particularly when more modern methods of treatment are applied, is extremely encouraging, and it is hoped that still better results may be obtained. Radical surgical procedures, including total cystectomy, should be reserved for those growths which have proved resistant to a thorough course of high voltage roentgen therapy and radium therapy.

Barringer [60] stated that the best statistics on carcinoma of the bladder indicate only between 25 and 30 per cent five year cures. This leaves a residue of 70 or 75 per cent of cases in which the patient succumbs to the disease. This means that one should not be satisfied with the present day methods of cure, and this is the reason new operative and irradiation devices are constantly cropping up.

When these cases are considered individually, total cystectomy comes first. Barringer stated that if the operation is performed, suprapubic implantation of the ureters is preferable to the implantation into the intestines, because it is less dangerous. There has been a distinct flare-up in extending the use of external irradiation to the treatment of carcinoma of the bladder. Pfahler has reported a few cures, but his pathologic reports are too inadequate to evaluate these. The statistics of operative removal are impressive. They indicate that the operative removal of carcinoma of the bladder has a definite place in the control of this disease. Its scope appears to Barringer to be limited. It does not seem to be applicable to tumors which involve the trigon too much. His impression is that more urologists in America are controlling vesical tumors by radium implantation than by any other method. Radium, with all its faults, and they are many, seems to be able to cure many tumors. Barringer's own trend is definitely away from the suprapubic implantation toward cystoscopic implantation. Further progress in the treatment of difficult infiltrating tumors is probably along lines which combine interstitial irradiation with external irradiation.

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[60] Barringer, B. S., in discussion on Colston and Leadbetter,[59] pp. 684-685.

Beer[61] stated that for papillary and infiltrating carcinoma partial cystectomy after electrocoagulation of the surface of the tumor, with or without ureteral transplantation into the bladder, or total cystectomy with implantation of the ureters into the skin or the sigmoid colon are undoubtedly the procedures of choice, and any one who is treating patients suffering from tumors of the bladder should be able to carry out these various procedures. Only by experience will the mortality of the operations in the latter group be diminished. The mortality at present is undoubtedly high for these surgical procedures, not only because the patients are old, as a rule, but usually because they have been neglected for a long time before they come to operation, have more or less damage to the upper part of the urinary tract and perhaps are suffering from local or distant metastasis.

In Beer's recent monograph on tumors of the bladder, a review of the later cases, plus those in his original report, confirmed his original conclusion presented at the International Congress at Brussels in 1927, and his results as far as five year cures are concerned are considerably better than those published by the Carcinoma Registry of the American Urological Association.

For instance, of 88 persons with papillary and infiltrating carcinoma of the bladder treated prior to 1930, 15 died. Of the 73 patients discharged from the hospital, 65 could be controlled. If one subtracts the 8 who were lost from observation and the 15 who died as a result of the operation or causes associated with the operation, 65 remain on whose cases one may base the efficacy of a radical surgical procedure, that is, partial resection with or without transplantation of the ureter. In this group of cases in which radical excision was done there were 24 five year cures, or 37 per cent, which is about twice that reported by Ferguson, based on the Washington Registry.

Moreover, in going over a series of cases in which total cystectomy was performed, the tumor having involved the trigon, both ureters and the neck of the bladder, it was found that in the cases in which operation was performed before 1930 there were 57 per cent permanent cures, which is by far the highest percentage, according to Beer, that could be obtained by any method of surgical approach, and is a most encouraging outlook for the future.

Beer stated that the outstanding conclusions one must draw from Dr. Ferguson's report are (1) that vesical tumors are very serious as a group, (2) that as yet there is no uniformity as to the proper method of treatment and (3) that the more radical the therapy the better is the chance of a permanent cure for the patient.

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[61] Beer, Edwin, in discussion on Colston and Leadbetter,[59] pp. 687-688.

In view of the fact that implantation of seeds of radon through the cystostomy wound has given five year cures in only 8.8 per cent of cases, whereas partial cystectomy of the bladder has given five year cures in 18.5 per cent, it must be evident that those who rely entirely *on the use of radium are not giving the patient with vesical tumor the* care he deserves. As has been repeatedly emphasized, every urologist should be able to treat vesical tumors by innumerable methods. For the simpler small tumors and papillomas and occasionally for papillary carcinomas, transurethral treatment with a high frequency current is surely the method of choice, though in the latter group radium seeds introduced transurethrally may be necessary to eradicate the disease.

Bothe[62] stated that a tumor of the bladder is occasionally well advanced before the patient is studied. In some cases the tumor is in a location that involves considerable risk for surgical removal, or it gives evidence of extensive infiltration. In such cases roentgen therapy should be of great assistance. In the papillary carcinoma the regression established by roentgen therapy facilitates subsequent interstitial irradiation. Irradiation has been used before electrocoagulation for the benign papilloma. It is generally agreed that many benign papillomas have been permanently destroyed by electrocoagulation alone. It is also a fact that follow-up examinations on patients with benign papilloma frequently reveal recurrence. It seems within the realm of possibility that preparatory high voltage roentgen therapy may reduce the incidence of this recurrence.

Higgins reported 5 cases of neoplasm which was primary in and confined to a diverticulum of the bladder in a series of 221 cases of tumor of the bladder which were seen at the Cleveland Clinic. Primary carcinoma of the urinary bladder frequently extends into and involves a diverticulum of the bladder, but a primary neoplasm in a diverticulum is a rather infrequent finding.

In the majority of cases diverticulum of the bladder may be diagnosed readily on cystoscopic and roentgenographic examinations. When blood can be seen spurting from the orifice of the diverticulum, the presence of a neoplasm should be suspected. In 2 cases, after thorough lavage of the diverticulum, persistent filling defects were noted on 2 successive examinations, and preoperative diagnoses were made which were verified at the time of operation. In 1 case the tumor was visualized at cystoscopic examination.

Total resection of the diverticulum containing the tumor is the rational treatment. Whether the intravesical or the extravesical technic is utilized depends on the preference of the surgeon. In this series the extravesical technic was used, and the diverticulum was excised completely with a portion of the bladder in the region of the orifice of the diverticulum. In 2 cases in which the ureters were contained in the wall of the diverticulum it was deemed advisable to divide and ligate the ureters and not attempt to reimplant them into the bladder. Although fulguration of the tumor has been employed, radical operation seems preferable.

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[62] Bothe, A. E.: Roentgen Therapy in the Treatment of Bladder Tumors, J. Urol. **36**:643-650 (Dec.) 1936.

In the 5 cases reported by Higgins,[63] 1 patient with papilloma of the bladder died of a cerebral embolism seventeen months after leaving the hospital, but the papilloma had not recurred up to that time. One patient with carcinoma in a diverticulum died suddenly of pulmonary embolism on the twenty-first postoperative day. One patient with carcinoma in a diverticulum lived one year and six months without recurrence. Another patient died of an unknown cause two years after removal of a diverticulum containing a papilloma. The fifth patient is living without recurrence six months after operation.

Diverticulum.—Babics[64] stated that 80 of 117 patients with a diverticulum of the bladder observed at von Illyés' clinic had some marked obstruction to the urinary outflow. Thirty-three were operated on. Stones were found in the diverticulum in 8, cancer in 4 and papilloma in 1. Five patients died after operation. The operative procedure has to be adapted to every patient. When the ureter ends in the diverticulum, it should be transplanted. This was done in 6 instances. Sometimes the kidney is so badly infected that it is better to remove it. Von Illyés when necessary performs a prostatectomy and diverticulectomy as a one stage procedure and has never noticed any disadvantage therefrom. One of these patients died from pneumonia after operation.

Cord Bladder.—Gill[65] gave a brief discussion of neurogenic dysfunction of the bladder with particular reference to cord bladder or that type of dysfunction of the bladder produced by disease of the spinal cord. Two cases of marked vesical paralysis are reported in patients whose only diseases were mild arteriosclerosis and severe diabetes mellitus of long standing. It is believed that the paralysis of the bladder was due either directly or indirectly to diabetes and its effect on the spinal cord, and the reasons for this belief are given. A close cooperation between the urologist, internist and neuropathologist is urged in the study of these extraordinary and unusual cases.

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[63] Higgins, C. C.: Neoplasms Primary in Diverticula of Urinary Bladder: Report of Five Cases, Am. J. Surg. **33**:78-84 (July) 1936.

[64] Babics, Antal: Ueber Blasendivertikel, Ztschr. f. urol. Chir. u. Gynäk. **42**:395-410, 1936.

[65] Gill, R. D.: The Diabetic (Cord) Bladder, J. Urol. **36**:730-739 (Dec.) 1936.

Munro[66] stated that for purposes of diagnosis, prognosis and treatment cord bladder resulting from all types of injury to the spinal cord should be divided into four distinct groups.

These may be measured cystometrically against the activity of the normal bladder in terms of initial and sustained tonus, the presence and periodicity of emptying contractions, the absolute amount of residual urine expressed in terms of percentage of fill, the storage capacity of the bladder and the reflex and voluntary sphincteric activity.

With these criteria, cord bladders may be classified as atonic, autonomous, hypertonic and normal.

The only permissible end-result of any cord bladder that is due to injury of the spinal cord is either an uninhibited cord bladder in cases of transection of the spinal cord above the sacral segments, an autonomous cord bladder in cases of destructive lesions of the sacral segments or cauda equina or a normal cord bladder in cases of all other types of injury to the spinal cord.

All types of cord bladder are amenable to treatment by tidal drainage, provided the apparatus is adjusted to suit the type of bladder. Except for complications due to misuse of the apparatus, tidal drainage as a method of treatment of cord bladder of any type has no contraindications. Rectal tubes used as indwelling urethral catheters, or mushroom catheters, may be employed indefinitely in conjunction with tidal drainage in either male or female urethras without producing cystitis or urethritis. They must be removed, cleaned and replaced once a week, and care must be taken to avoid the use of those that are too large.

The incidence of decubitus ulcerations is greatly reduced, and the problem of nursing a patient with an injury to the spinal cord is greatly simplified if the patient is kept dry by the proper use of tidal drainage. The incidence of all types of sepsis of the urinary tract in cases of injury of the spinal cord has been reduced from 73 per cent in 33 cases to 15 per cent in 26 cases through the prompt, intelligent and routine use of tidal drainage in the care of the bladder.

Conditions of the Neck of the Bladder.—MacKenzie and Beck,[67] from a comparison of the 30 specimens of the adult female urethra and the neck of the bladder with 17 similar specimens from children 4 years of age and younger, concluded that chronic inflammation of the urethra and the neck of the bladder is present in a higher percentage of adults than has heretofore been imagined. Perimucosal structures about the neck of the bladder and the posterior third of the urethra are acquired. These structures simulate prostatic tissue because they take origin from the same type of embryologic tissue and thus have the same inherent properties. The stimulus required for the acquisition of these structures may be: (1) infection within the genito-urinary tract, (2) structural anomalies within the genito-urinary tract and (3) trauma at childbirth. These buds and nests, known as von Brunn's cell nests or buds, so far as they are a proliferation of the mucosal epithelium derive their lumens from the intra-epithelial glands, as seen in the mucosal epithelium in children. Those structures about the neck of the bladder and the posterior third of the urethra, referred to by previous workers as prostatic structures, are considered by MacKenzie and Beck to result from a process similar to cystic disease of the upper part of the genito-urinary tract, better known as pyelitis cystica, ureteritis cystica and cystitis cystica, according to location. They propose to call it cystitis cystica when it occurs about the neck of the bladder and urethritis cystica when it occurs in the urethra.

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[66] Munro, Donald: "The Cord Bladder:" Its Definition, Treatment and Prognosis When Associated with Spinal Cord Injuries, J. Urol. **36**:710-729 (Dec.) 1936.

[67] MacKenzie, D. W., and Beck, Sidney: A Histopathological Study of the Female Bladder Neck and Urethra, J. Urol. **36**:414-437 (Oct.) 1936.

Pilcher[68] reported the case of a woman aged 49 who had a malignant lesion in the bladder situated close to the neck. Complete surgical removal of this lesion necessitated resection of most of the trigon of the bladder and division of the urethra about 1.5 cm. distal to the internal sphincter. Resection of the urethra involved the region that is normally occupied by the external sphincter in the male. The distal end of the urethra was then sutured to the remaining portion of the trigon and wall of the bladder, and the neck of the bladder was reconstructed around a catheter. Convalescence was uneventful. After removal of the suprapubic tube, the suprapubic sinus healed promptly. The patient voided satisfactorily and was not incontinent. Urination was comfortable and under perfect control. A surgical procedure of this type at once raised the question of whether or not incontinence would result. Cabot, in discussing Pilcher's report, stated that there is considerable confusion regarding the external urethral sphincter of the female. Some authors describe the external sphincter as the more powerful of the two and as a thoroughly well defined structure. Other authors doubt the existence of such a structure. Recent microscopic studies of longitudinal sections of the urethra made by Shoemaker failed to reveal definitely placed circular fibers such as are regularly to be found in the position of the external sphincter in the male. The fact that incontinence did not result in this case suggests that the control of the urine after complete removal of the internal sphincter may depend on the widely scattered circular muscle fibers rather than any well defined muscle group properly described as an external sphincter.

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[68] Pilcher, Frederick, Jr.: Complete Resection of the Vesical Neck in the Female, Proc. Staff Meet., Mayo Clin. **11**:577-579 (Sept. 9) 1936.

Heitz-Boyer[69] applied the name "inflammatory new growths of the neck of the bladder" to a combination of pathologic conditions at that point which he has been clearly recognizing for the last fifteen years and which appear almost exclusively in the female, corresponding to lesions, often minimal in size, of the urethrocervical region. These new growths, which appear as small eminences of various degrees, not only may lead to intractable cystitis but may result in grave disturbances of the general health of the patient. Of an inflammatory nature and occurring after prolonged infection of, or toxic effect on, the cervico-urethral mucosa, they may be of enterorenal, staphylococcic or venereal origin. They can be diagnosed only endoscopically and can be recognized as representing any one of five different varieties, namely, polypous, cystic edematous or angiomatous or of the nature of an abscess.

Treatment must be surgical and consists of the application of the high frequency current in the form of etincelage, with the author's forked electrode; this is not a cutting current, nor yet an electrocoagulation, both of which are too drastic. Destruction of each eminence may be supplemented at will by electric curettage of the entire neck of the bladder, if there is pathologic change between the individual outgrowths; but this must be done with the greatest care, with control rigorously maintained at low heat. The results are beyond all expectation; in nearly all cases the patients are entirely cured after two or three months of application. When failure results, it is because the new growths were not the primary cause of the trouble but were the result of a neuropathic diathesis.

Rupture.—Dixon and Strohl[70] reported a case of rupture of the urinary bladder. This case serves to emphasize the importance of surgical intervention in acute abdominal disorders when certain signs, such as acute pain and generalized rigidity, are present. The character of the fluid in the abdominal cavity, although it is no different in appearance than that frequently found in cases in which ascites occurs as a result of a variety of causes, suggested the possibility of urine from a ruptured bladder.

The cause of rupture of the bladder in this case is not known. The patient said that he had voided 3 or 4 ounces (90 to 120 cc.) of urine soon after the onset of the acute pain in the upper part of the abdomen and that he had voided before retiring, eight or nine hours previously.

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[69] Heitz-Boyer, M.: La maladie néoformante du col de la vessie chez la femme, J. d'urol. **42**:216-251 (Sept.) 1936.

[70] Dixon, C. F., and Strohl, E. L.: Spontaneous Rupture of Urinary Bladder, Am. J. Surg. **33**:110-113 (July) 1936.

The urine obtained by passage of a catheter three or four hours before operation evidently came from the abdominal cavity. The edges of the opening in the bladder were ragged and appeared necrotic. They were trimmed until healthy-appearing tissue was reached. Unfortunately, the excised portion of the wall of the bladder was not preserved for microscopic study. Syphilitic ulcerations do have a tendency to occur in the midline; for instance, ulcerations in the midline of the anterior thoracic wall and sternum are seen occasionally. In such instances syphilis has always to be ruled out as a possible etiologic factor. In this case the rupture was in the midline, and obstruction of the neck of the bladder was not a factor, as it previously has been reported to be in some of the cases.

Incontinence.—Lowsley[71] stated that it is possible to cause rupture of the bladder in animals if the urethra is tied tightly with ribbon gut. Ribbon gut tied around the urethra with moderate tightness will cause stricture and accompanying distention of the bladder and thinning of the wall. If the ribbon gut is applied more loosely, the bladder will succeed in emptying itself against pressure, resulting in marked hypertrophy of the musculature and contraction of the bladder. No hydroureter or hydronephrosis resulted from these experiments. The animals were killed or died two months or less after the operation.

In the human being, various muscle transplantations are replaced by the formation of an efficient sphincter by means of ribbon gut, used as an encircling band, a plication suture over the top of the relaxed urethra in the female or as a plication of the membranous urethra in the male. In cases of partial incontinence a cure is effected by encircling the urethra with ribbon gut and tying it snugly. Fibrous tissue replaces the ribbon gut, as was demonstrated by the experiments on animals. The newer plastic operations, made possible by the use of ribbon gut, are more desirable than the older procedures because they make counterdrainage unnecessary, thereby decreasing the period of hospitalization.

Fistulas.—Higgins[72] reported from a review of the literature that vesico-intestinal fistulas are caused more frequently by an inflammatory process than by carcinoma or trauma. Diverticulitis of the bowel is the most frequent etiologic factor. A preliminary colostomy is advisable in cases in which the causative factor of the formation of fistula is diverticulitis of the colon. The most common sites of the fistulas were between the rectum and the bladder and between the sigmoid and the bladder. A diagnosis may be established by cystoscopic and proctoscopic examination and the employment of cystograms and enemas of barium sulfate. Radical operation is essential in dealing with a fistula associated with a malignant growth. Prognosis depends on the etiologic factors associated with the formation of the fistula. Treatment is essentially surgical.

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[71] Lowsley, O. S.: New Operations for the Relief of Incontinence in Both Male and Female, J. Urol. **36**:400-413 (Oct.) 1936.

[72] Higgins, C. C.: Vesico-Intestinal Fistula, J. Urol. **36**:694-706 (Dec.) 1936.

Drainage.—Boyd[73] stated that suprapubic cystotomy can be performed with the patient under local and field block anesthesia, which is so much safer for the patient who is a poor risk than any type of general or spinal anesthesia. Suprapubic cystotomy insures a dry wound in practically every case, and if there is any leakage, it is slight and can be controlled readily. It nearly always prevents the development of any except mild infections of the wound. It permits decompression of the bladder and opening the bladder when necessary without distention by air or fluid. It prevents postoperative changes in the symphysis pubis and, as far as can be done, the later separation of the muscles with the formation of hernia. It does not require long experience in operations of the bladder.

The essentials in technic are as follows: A midline incision is made. The fat and fascia from the upper, anterior part of the bladder over an area from 4 to 6 cm. in diameter are freed. The incision in the bladder about the tube is closed with interrupted plain catgut sutures. The bladder is infolded for from 2 to 2.5 cm. with a second layer of sutures. The tube then lies in the middle of the closed incision, and the bladder is not sutured tightly about the tube. The bladder is anchored to the abdominal wall if the capacity of the bladder is large. One large silver wire stay suture is used to approximate the rectus muscles. A small rubber tissue drain passing all the way through the abdominal wall should be left in the upper end of the wound. Closure of the lower 2 to 3 cm. of the wound is not done, and a small piece of fenestrated Dakin tube should be left in that part for drainage.

The postoperative care consists of daily dressings wet with acriflavine and continuous or decompression drainage. The upper and lower ends of the wound are gently opened daily with a hemostat for as many days as necessary to insure adequate drainage.

There were no fatalities in a series of 60 cases, even though some of the patients were very ill, and only 1 had an infected wound. A few superficial, unimportant infections developed about the drains. Thrombosis of the iliac vein occurred in 2 very feeble old men. There have been no hernias or other complications.

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[73] Boyd, M. L.: Suprapubic Cystotomy for Drainage, J. Urol. **36:**740-755 (Dec.) 1936.

PENIS

Tuberculosis.—Lazarus and Rosenthal[74] reported a case of primary tuberculosis of the penis occurring in a young adult after sexual exposure. Radical amputation of the penis was necessary. This condition is a rare clinical lesion, particularly in adults. Only 25 cases have been reported in the literature to date. The diagnosis is often confused with chancroid, chancre or granuloma inguinale and therefore is made late in the course of the disease. It can be confirmed only by histologic study, preferably by inoculation of an animal. The disease is characterized by a slowly spreading, painful ulcer with an indurated border which has a marked tendency to become undermined and by a central ulceration covered with a yellowish, odorless slough. In the later stages areas of necrosis may be seen near the indurated margin and nodules in the region of the base of the ulcer. The lesion shows a tendency to scar formation, which at times breaks down to form new ulcers and is resistant to all types of treatment. Inguinal adenopathy is generally present but is never an outstanding feature of the disease. Urinary symptoms occur only when the urethra is involved.

In several cases excision or curettage of the lesion associated with the usual hygienic regimen for generalized tuberculosis produced good results. Radical amputation is done in cases in which the glans penis and urethra are extensively involved. The prognosis is favorable in primary tuberculosis of the penis in adults. When it occurs in children after circumcision, the prognosis is unsatisfactory.

URETHRA

Hypospadias.—Walters[75] stated that the most successful operations for hypospadias have been those in which flaps of skin taken from the penis or scrotum have been used to form a skin-lined canal to the end of the penis from the abnormal opening of the urethra. Operations intended to overcome the penile curvature deformity of hypospadias should be undertaken at a very early age, preferably between 1 and 2 years. Ordinarily this correction can be satisfactorily obtained by means of transverse incisions through the fibrous cord occupying the position of the absent penile urethra, one transverse incision being made immediately in front of the abnormally placed meatus and one relatively far forward close to the glans penis, if a second one is required.

There are three types or degrees of hypospadias: (1) perineal, when the abnormal opening is in the perineum; (2) penoscrotal, when it is at the root or base of the penis, and (3) penile, when it is in the shaft of the penis. The method of Ombrédanne is applicable to all three types of hypospadias and has the advantage that the penile portion of the flap which is used to form the urethra is free from hair. The principles of treatment of hypospadias, as outlined by Ombrédanne, consist in converting a perineal or penoscrotal opening to a penile opening by elevating a longitudinal flap of skin from the scrotum distal to the urethral opening and reflecting it upward; covering it with lateral flaps taken from the adjacent areas of the scrotum.

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[74] Lazarus, J. A., and Rosenthal, A. A.: Primary Tuberculosis of the Penis, J. Urol. **35**:361-377 (March) 1936.

[75] Walters, Waltman: Successful Operations for Hypospadias, Ann. Surg. **103**:949-958 (June) 1936.

In the Bucknall operation a delayed flap of skin is raised from the scrotum, forming the anterior portion of the skin-lined canal, which extends from the penoscrotal or penile hypospadiac opening to the end of the penis. Its greatest value is in cases in which other methods have failed, and this is most likely to be in those in which the patients are adults. Healing takes place without the development of a fistula because of the wide attachment of flaps adjacent to the skin-lined canal and the absence of tension on the anastomosis from erections during convalescence, due to the elasticity of the scrotum.

The Thiersch operation in which parallel flaps are taken from the penis gives excellent restoration of the canal unless a fistula develops. It employs tissue free from hair and of fine texture, which is consequently particularly well suited to its changed environment. Unfortunately, it has been characteristic of this type of operation that the formation of a fistula was a relatively common complication, requiring further operations for its repair, oftentimes with unsuccessful results.

Various stages of the Ombrédanne operation have been used, a total of 88 procedures for 32 patients. It was necessary, therefore, in order to obtain a satisfactory end-result to use an average of three stages. The cases were divided about equally into those of perineal, penoscrotal and penile hypospadias. The results in 28 of the 32 cases were excellent. The Bucknall type of operation has been used in 16 cases, and here likewise the operation has of necessity been divided into two stages, to which has been added narrowing of the urethral orifice by the method of Ombrédanne. The results of operation in these cases were excellent. The Thiersch method and its modifications have been used in 13 cases, 46 different procedures being employed in these cases to complete the operation.

Urethral Glands.—Cabot[76] stressed the conflicting opinions that have existed for a number of years regarding the possibility of lesions of the urethra of the female acting as a focus of infection similar to certain lesions of the prostate and cervix. The evidence in regard to the existence of important glandular structures in the proximal two thirds of the female urethra has been inconclusive.

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[76] Cabot, Hugh: Are Glands in the Posterior Urethra of the Female an Important Focus of Infection? Proc. Staff Meet., Mayo Clin. **11:**589-591 (Sept. 9) 1936.

The conclusion from the recent studies of MacKenzie and Beck[77] and of Cabot and Shoemaker[78] on more than 100 specimens removed at postmortem examination was that there are no glandular structures in the proximal two thirds of the female urethra. One of the striking observations in Cabot and Shoemaker's study was the number of very deep crypts in the mucosa, which when seen in cross-section might be mistaken for glandular structures if care were not exercised in studying the arrangement of the cells; these were in fact only simple invaginations of the urethral mucosa.

In the specimens studied a large number of cysts containing albuminous material were found lying beneath the mucosa. According to Cabot, these are the areas which have been referred to by Renner and by Folson as showing what they regarded as corpora amylacea. The cysts were lined with squamous epithelium and showed no evidence of glandlike structures. They appeared to be entirely similar to the structures seen in the well known conditions of pyelitis, ureteritis and cystitis cystica. In other words, they demonstrated that cystic disease, well recognized in other parts of the urinary tract, is very common in the urethra. Papillary outgrowths in the posterior portion of the urethra were frequently noted. That there are many symptom-producing lesions of the female urethra is an undoubted fact, but the evidence does not warrant assuming that such lesions originate from glands or that they can be made the basis for relapsing infection of the urinary tract in the female. The author expressed the belief that the hypothesis advanced by Renner and by Folsom of a major focus of infection in the posterior part of the urethra of the female comparable with lesions of the prostate of the male has no satisfactory basis in anatomic fact.

Urethral Lymphatics.—Parker[79] made a study of the lymph vessels from the posterior part of the urethra and stated that the distribution of the lymphatics from this portion and their regional lymph nodes varied for the most part according to the variations in the pelvic arterial branchings.

In 30 stillborn male infants the lymph channels coursed backward along the main pelvic arteries most frequently to nodes situated along the pubic branches of the obturator arteries, to nodes of the internal, middle and external chains of the external iliac groups and to hypogastric nodes, and, occasionally, to lateral sacral nodes, to ischiatic nodes of the gluteal region and to superior hemorrhoidal nodes.

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[77] MacKenzie, David, and Beck, Sidney: A Histopathologic Study of the Female Urethra, to be published.

[78] Cabot and Shoemaker: Unpublished data.

[79] Parker, Alice E.: The Lymph Vessels from the Posterior Urethra. Their Regional Lymph Nodes and Relationships to the Main Posterior Abdominal Lymph Channels, J. Urol. **36**:538-557 (Nov.) 1936.

The lymph vessels and nodes draining the postpubic portion of the urethra in the female differed somewhat in distribution from those found in the male. The lymph vessels coursed backward along the umbilical arteries, followed branches and trunks of the hypogastric arteries and traversed the pelvic fascia along the lateral borders of the bladder. The regional nodes for the efferent lymph vessels following those courses were nodes of the internal and middle chains of the external iliac groups, hypogastric nodes, lateral sacral nodes and ischiatic nodes of the gluteal regions.

Indirect and direct connections between lymphatics of the posterior part of the urethra and of the wall of the bladder are described. The courses of extension of injected material from the regional nodes through the posterior abdominal lymph channels to the thoracic duct are illustrated. Some of the lymph nodes, found to be regional or intercalated nodes of the efferent lymph vessels of the posterior part of the urethra, are apparently identical with lymph nodes described in the literature as regional or intercalated nodes for other pelvic organs and regions but were never previously connected with this portion of the urinary tract. Most of the regional nodes for the posterior part of the urethra belong to the principal groups of nodes of the pelvis.

Urethral Tumors.—Campbell and Fein [80] reported a case of malignant melanoma of the penile urethra which is a clinical novelty and of special pathologic interest. Sarcoma of the urethra most commonly manifests itself by the appearance of a localized neoplasm at some point along the canal. As the growth enlarges, symptoms of obstruction of the lower part of the urinary tract appear. In 4 of the cases reported in the literature a gonorrheal stricture was erroneously believed to be present. With secondary infection of the tumor, the symptoms were suggestive of periurethral abscess, as they were in the case cited by Campbell and Fein. Inguinal adenitis is attributable to metastasis and to lymphatic absorption from the region of the tumor. As the disease progresses, metastasis elsewhere is likely to be noted, even in the cervical region. Ultimately these patients died of neoplastic toxemia or of renal failure.

The diagnosis of tumor of the urethra is suggested by the history of a periurethral swelling in the absence of local infection. The growth is usually firm. As in this case, regional metastasis may offer a diagnostic clue. Diagnosis may be confirmed by the histologic examination of a small piece of the tumor removed with a biopsy rongeur introduced through a tubular endoscope. This may be accomplished readily without risk or marked discomfort to the patient. Prognosis is almost uniformly hopeless. Wide excision of the growth offers the only posssibility of cure, but because of the high degree of malignancy of these tumors of the urethra and their tendency to metastasize, surgical intervention almost always proves futile. Intensive radiation therapy, either by interstitial implantation or with the roentgen rays, offers the only aid to surgical treatment, but for similar reasons will also fail.

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[80] Campbell, M. F., and Fein, M. J.: Malignant Melanoma of the Penile Urethra, with a Brief Review of Urethral Sarcoma in the Male, J. Urol. 35: 573-582 (May) 1936.

Urethritis.—Gurnee[81] stated that the principles which govern the treatment of gonorrhea in the male should be just as forceful in the female, but because of the absence of pain the tissues are subjected to strong caustics or electric cautery instead of gentle daily manipulation.

Complete shutting off of gonococci results in their death. Curtis has proved this phenomena in tubo-ovarian abscess, and it has been observed to hold true in bartholinitis; the organism dies in about three weeks if there is no exit for the pus. Incomplete drainage of gonococcic pus results in retarded cures.

By means of the Elliott apparatus a consistently uniform temperature of 128 F. can be maintained for any length of time against a large portion of distended vagina, cervix, adjacent parametrium and pelvic organs, thereby clearing up the latent foci of infection which heretofore were so difficult to reach. Fever therapy with the hot cabinet alone gives only a 55 per cent chance of cure of gonorrhea and is a very drastic treatment. Short wave diathermy, while it gives sufficient heat, is extremely dangerous when used in combination with the hot cabinet for fever therapy. Fever therapy can best be given without any serious complications by combining the hot cabinet and the Elliott treatment.

Owens[82] considered that by treatment with artificial fever, prompt and dramatic relief of gonococcic arthritis and acute epididymitis can be promised in every instance. Owens stated that this progress in therapy is most appreciated as it applies to arthritis, which was formerly so painful, time consuming and often permanently disabling.

Acute urethritis of less than two weeks' duration has not responded to fever treatment as well as have the chronic infections with prostatic involvement. This experience suggests the possibility that fever therapy alone should not receive all the credit for the apparent cures and that natural resistance in the cases of acute infection has not yet developed the antigenic factors that are probably more active in the cases of chronic infection.

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[81] Gurnee, W. S.: Gonorrhea in the Adult: Diagnosis; Elliott Treatment and Hyperpyrexia, Am. J. Surg. **33**:500-508 (Sept.) 1936.

[82] Owens, C. A.: The Value of Fever Therapy for Gonorrhea, J. A. M. A. **107**:1942-1945 (Dec. 12) 1936.

Clinical experience is accumulating to support the laboratory conclusions that certain strains of gonococci may be utterly destroyed by temperature of a degree and duration tolerable to the patient, while other strains are resistant to such temperatures. An increasing number of patients have achieved apparent cure after a single session of six hours at a temperature of 106.5 F., while others receive no appreciable benefit after four sessions.

Given patients who can and will take the treatment, more than 80 per cent of gonococcic infections regardless of complications may be absolutely cured in two weeks. Ability of the patient to take the treatment depends on the condition of the heart, the resistance of the skin to heating and the patient's temperament. Those who are unsuitable for one reason or another constitute 12 per cent in Owens' series.

Urethral Injury.—O'Conor[83] stated that in a period of thirteen years he treated 31 men suffering from traumatic rupture of the urethra. Eight incurred this injury from falling astride a loose manhole cover. He stated that although no mention of injury from this source is to be found in the textbooks, personal inquiry has disclosed that in the larger metropolitan centers it occurs sufficiently often to deserve comment. The blow received by the perineum is especially severe, because the metal cover is swung violently upward and strikes as the body is lurching downward and forward. In the 8 patients so injured, the posterior bulbous urethra, close to the triangular ligament, received the impact. In none was the pelvis or other bones fractured. When the urethral floor is so severely traumatized that continuity is destroyed, the proximal (vesical) portion is retracted and elevated by the pull of the strong fascial attachments to the urogenital diaphragm. The extent of the separation of the torn urethral edges depends largely on whether the floor of the urethra is severed or whether the roof alone is torn across. If the floor alone is injured and the roof of the urethra is intact, one may be fortunate enough to guide a small, soft rubber catheter (Wishard), passed over a fairly rigid stylet, by careful and close adherence to the roof of the urethra during the insertion. When this procedure is successful, drainage of the bladder is supplied by the indwelling catheter, and unless there has been perineal extravasation or marked hemorrhage, no incision is necessary. If perineal extravasation or hemorrhage has occurred, single or multiple incisions in the perineum with adequate provision for drainage will suffice, and the urethral lumen will restore itself along the indwelling catheter.

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[83] O'Conor, V. J.: Repair of Rupture of the Male Urethra, with Report of Eight Injuries from Falling Astride a Manhole Cover, Surg., Gynec. & Obst. **63**:198-200 (Aug.) 1936.

Except in instances of crushing injury of the floor of the urethra without separation of the urethra at the point of injury, catheterization, even carefully and expertly done, is rarely possible. It should be emphasized that repeated unsuccessful attempts at catheterization only increase the local injury and add to the dangers of increased hemorrhage and deep-seated infection.

In all cases of rupture of the urethra from external violence, the ease of repair and the rapidity of recovery depend largely on the avoidance of unsuccessful catheterization and the recognition of the necessity for immediate surgical intervention.

Until recently O'Conor favored the perineal approach in draining the bladder and in attempting properly to restore the urethral lumen. Although patients so treated did well and usually enjoyed a somewhat shorter period of hospitalization than those treated suprapubically, the resultant perineal and urethral scarring was always considerable and necessitated frequent and repeated urethral dilation for a prolonged period. The method now preferred is extraperitoneal cystotomy, with retrograde splinting of the urethra by an indwelling catheter and perineal incision only when necessary to drain extravasated blood and urine. This splinting is accomplished by the use of interlocking sounds which are passed simultaneously through the posterior and the anterior part of the urethra and joined in such a way that the urethral sound may be guided safely into the bladder. A no. 22 French soft rubber catheter is then stitched securely over the end of the urethral sound and withdrawn through the urethra. The catheter is properly fixed in the urethra, and the bladder is closed in the usual manner with a small mushroom catheter in the dome for immediate drainage. The urethral catheter is closed for a period of from five to seven days, suprapubic drainage being allowed during this time. The urethral catheter is then opened, the bladder is irrigated and the suprapubic tube is removed. There is rarely any suprapubic leakage of urine after this time, as drainage is adequately supplied through the urethral catheter. This is removed when the suprapubic wound seems firmly healed, usually on the twelfth to the sixteenth day after operation. The complete restoration of normal urinary function and the subsequent lack of urethral stricture are the obvious advantages of this method. These patients require occasional urethral dilation, to be sure, but they do not present the serious problem of potential stricture that is almost invariably present after perineal urethrotomy.

TESTIS

Ectopia.—Deming,[84] after a series of experiments with monkeys, stated that the gonadotropic factor is a definite aid preceding and following surgical treatment of the undescended testis. It enlarges the inguinal canal and the cord and renders the testis more movable in the monkey. Treatment may be instituted in the human being as early as 2 years of age. The earlier the treatment the better are the chances for a normally functioning testis. The histologic picture in the monkey six weeks after the cessation of the administration of the gonadotropic factor persists with negligible change.

Woodruff and Milbert[85] reported a case of strangulation of an undescended testis by a loop of omentum. It represents a rare and previously unrecorded complication threatening the safety of the maldescended organ. Etiology, pathology, symptomatology, diagnosis and treatment are discussed as they pertain to the condition in question. In this instance it is rather ironical that the omentum, so frequently referred to as the "policeman of the peritoneal cavity," should have wandered astray to become the "hangman" of the testis.

Cysts.—Abell[86] reviewed cysts of the testis, excluding hydroceles of the tunica vaginalis, encysted hydroceles of the cord and those occasionally noted in the body of the testis proper; they arise within epididymal structures or vestigial remnants connected with them. Abell observed 32 instances of cysts conforming to this in origin and site.

Four patients gave a history of trauma with the appearance of the tumor immediately thereafter. One other stated that the tumor appeared after the wearing of a truss and still another that it developed after an operation for hernia.

The size was noted in 26 cases; the smallest tumor was 1 inch (2.5 cm.) in diameter, and the largest measured 8 by 4 by 4 inches (20 by 10 by 10 cm.); the size of the remainder varied between these limits. Twenty-five of the 32 patients came to operation, the character of the growth being unilocular in 12 cases, multilocular in 9 and polycystic in 4; 21 were unilateral and 4 were bilateral; 3 were enclosed within the tunica vaginalis or were intravaginal, and 22 were extravaginal. Twenty-six operations were done on 25 patients, 1 patient returning after fourteen years with recurrence of the cyst in the site of the former operation.

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[84] Deming, C. L.: The Gonadotropic Factor as an Aid to Surgery in the Treatment of the Undescended Testicle, J. Urol. **36**:274-288 (Sept.) 1936.

[85] Woodruff, S. R., and Milbert, A. H.: Strangulation of the Undescended Testicle by a Loop of Omentum, J. Urol. **36**:558-563 (Nov.) 1936.

[86] Abell, Irvin: Cysts of the Testicle. Ann. Surg. **103**:941-948 (June) 1936.

The pathologic report revealed polycystic disease in 4 cases, which was bilateral in 2 and unilateral in 2. Specimens from 1 case of bilateral polycystic disease were unusually large, measuring 170 by 60 by 40 mm. and 150 by 50 by 30 mm., respectively. Of the specimens from the cases of bilateral involvement, only 1 showed recognizable epididymal tubules, being composed of pale pinkish gray fibrous and serous tissue containing many simple thin-walled cysts clumped together in masses. The cysts varied in size, measuring from 2 to 40 mm. in diameter, and contained clear, colorless fluid. The unilateral specimens were similar in character. In some of the cysts the walls were hyalinized and vascularized and revealed lymphocytic infiltration.

These cysts may be considered as falling in three groups: (1) cysts having their origin in vestigial remnants, (2) retention cysts and (3) polycystic growths or cystic embryomas.

URINARY CALCULI

Gray[87] reported a series of clinical cases of stone in the urinary tract from the Lester Chinese Hospital in Shanghai. He stated that infection played little part in the etiology and that it certainly is not an essential feature. The reaction of the urine has also not been of great significance. In the experimental cases, although the tendency has been for the urine to become alkaline, stone may form before this happens.

The two positive findings which have been observed throughout the study have been: (1) some alteration in the metabolism, so that the urine may be considered to be supersaturated with stone-forming substances and the formation of sediment would therfore be likely, and (2) a local factor in the urinary tract. It is felt that the latter probably acts by altering in some way the colloid conditions, so that the sediment becomes a concrement. It is suggested that in most cases this factor has been some alteration in the integrity of the epithelial lining of the tract. Such a change may easily be produced experimentally by trauma, obstruction, perhaps infection, devitalization by means of injury to the vascular supply, chemical irritation and a diet deficient in vitamin A. The last-named factor needs to be of a severe grade, but if it is it will produce a series of changes of which the last stage is keratinization. Formation of stone may occur in the presence of either of these factors singly, but much more readily in the case of the second. In the clinical cases it is felt that such alterations in the epithelium might well occur, and a number of biopsies of the mucosa of the bladder have been made. With the exception of 2 cases, however, although changes have been noted, they have not approached the severity of those obtained by experimental means, especially by the diet deficient in vitamin A. Neither has there been any other evidence in a survey of the diet or in the clinical condition of the patients to suggest more than at most a slight deficiency in vitamin A. However, it was shown experimentally that with the diet stone may form before the epithelial change has progressed as far as as keratinization. This was particularly true if an excessive quantity of vitamin D had been added to the diet.

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[87] Gray, J.: Urinary Stone Formation, Clinical and Experimental, Chinese M. J. **50**:761-786 (June) 1936.

As a large number of the patients have been children or members of the laboring class who work in the open without many clothes, it was felt that the possibility of a moderate excess of absorption of vitamin D must be considered, or perhaps a combined deficiency of vitamin A with an excess of vitamin D. Apart from this, although the number of clinical cases investigated is not yet large enough, the evidence does not point strongly to a deficiency of vitamin A of any severe grade.

The effect of polishing rice, particularly in regard to the possibility of calcium dust being mixed with the food, is felt to be of importance in Eastern countries.

Hou,[88] in his experiments on albino rats, showed that the addition of vitamin D to a diet which was deficient in vitamin A and in fat increased the incidence of urinary calculi and the removal of vitamin D decreased it. Alteration of the protein content of the diet also affected the frequency of formation of urinary calculi. Both a high and a low casein content resulted in an increase in the number of cases of calculi up to 100 per cent. Chemical analysis of the proteins for calcium and phosphorus indicated that the result was not due to an unbalanced calcium and phosphorus ratio. A lowering of the inorganic calcium and phosphorus in the diet caused an increase of the incidence of urinary calculi. The addition of heated lard caused a decrease in the frequency of calculi. Rats on the diet low in calcium and phosphorus, however, showed an increase.

In general, among the different groups studied the occurrence of calculi appears to run parallel to the presence of infection or of severe changes in the epithelium of the kidney and the urinary bladder. The presence of calculi in the kidney or in the bladder bears some definite relation to the type of diet used.

The calculi found in the various groups studied consisted mainly of triple phosphates.

Snapper, Bendien and Polak[89] stated that urine contains many salts and compounds in solution, some of which are hardly water soluble, such as uric acid and calcium oxalate. This condition is brought about by two factors: (1) the hydrotrophic action of certain substances, such as urea and hippuric, salicylic and mandelic acids, which further the solubility of insoluble salts, and (2) the presence of colloids. For example, 100 cc. of water will dissolve 0.63 mg. of calcium oxalate, while 100 cc. of a 3 per cent solution of urea will dissolve 1.28 mg. Likewise 100 cc. of water will dissolve 0.8 mg. of calcium carbonate, while a like amount of 15 per cent sodium salicylate will dissolve 5 mg. The benzoates, hippurates and mandelates have the same property.

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[88] Hou, H. C.: The Influence of Diet on the Formation of Urinary Calculi, Chinese M. J. **50**:787-796 (June) 1936.

[89] Snapper, I.; Bendien, W. M., and Polak, A.: Observations on the Formation and the Prevention of Calculi, *Brit. J. Urol.* **8**:337-345 (Dec.) 1936.

In the development and growth of renal stones, precipitation of flocculation of the colloids which form the nucleus and frame of the stone is more important than the precipitation of salts, which is secondary. Therefore, calculogenesis and growth may be inhibited by stabilizing the urinary colloids; without precipitation of the colloids no renal stone can develop or increase in size. The authors have shown that in vitro the salicylates will prevent precipitation of different colloids by aluminum sulfate, and that other salts, such as the hippurates, the benzoates and the mandelates, are less effective in this respect. Because hippuric acid has the property of hydrotrophy and also inhibits flocculation of colloids, the authors considered that its presence in the urine assumes new importance.

In experimental calculosis brought about by the use of a standard diet with vitamin A but with large amounts of calcium carbonates (3 per cent) they prevented the formation of stones by the use of large amounts of sodium benzoate, which is excreted in the urine linked with amino-acetic acid as hippuric acid. They also cleared up clinical phosphaturia without changing the reaction of the urine by giving 6 Gm. of sodium benzoate daily. They attributed this to the hydrotropic property of hippuric acid and concluded that the use of this substance is a rational measure in preventing recurrent calculi. Hippuric acid was used because it is a physiologic constituent of the urine. Other stabilizing and hydrotropic substances, such as the salicylates and mandelates, may give even better results.

Kretschmer[90] reported that of 21 children with stone in the urinary tract, 4 did not undergo treatment. Three of these passed stones spontaneously. The fourth was a girl with a large stone in the kidney, for which surgical intervention was advised but was refused.

In 5 cases stone was removed from the kidney by pyelolithotomy and in 1 by nephrolithotomy; in 2 cases resection of the kidney was also carried out. The patients with stone in the ureter were treated by ureterotomy. Five of the patients with stone in the bladder were treated by suprapubic lithotomy, and 5, by litholapaxy. There were no deaths and no postoperative complications.

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[90] Kretschmer, H. L.: Stone in the Urinary Tract in Children: A Critical Study of Twenty-One Cases, Am. J. Dis. Child. **52**:513-527 (Sept.) 1936.

The indications for the treatment are the same in the child as in the adult. If the stones are small enough to pass, if they produce only slight evidence of obstruction or none at all and if infection is mild or absent, medicinal management is justifiable, that is, the administration alternately of urinary antiseptics and alkaline diuretics. The child should be encouraged to drink large quantities of water, milk, lemonade and other liquids. When the stone in the kidney or the ureter is large, so that it produces definite obstruction, or when there is profuse blood, infection or repeated attacks of renal colic, the patient should be operated on.

SURGICAL TREATMENT FOR UROLOGIC CONDITIONS

Priestley and Counseller[91] stated that during 1935 there were 764 patients with urologic conditions on whom 917 operations were performed. These 917 operations included 1,555 surgical procedures. There were 14 deaths in the entire group, or a mortality of 1.8 per cent of the total patients operated on. Hydronephrosis, nephrolithiasis and tumors constituted most of the conditions for which operation was performed. Included in this group were certain patients with far advanced disease. Conservative surgical procedures in selected cases of hydronephrosis are now fairly well standardized and yield satisfactory results in the majority of cases. Nephrolithiasis is a condition which still presents many problems, especially regarding etiology and the prevention of recurrence. In this series 32 renal tumors were removed without a death. Some very large neoplasms were extirpated satisfactorily after preliminary roentgen therapy. Occasionally the anterior approach to the kidney was employed.

Of 57 patients with ureteral lithiasis, transurethral manipulation of the stone or stones was performed on 44 per cent and ureterolithotomy on the remainder. Rather definite indications exist for each procedure, and the best results are obtained by judicious selection of patients for each method. Transplantation of one or both ureters to the sigmoid colon was performed on 13 patients because of various lesions of the bladder, with 2 deaths. Three patients were subjected to transplantation of one or both ureters to the skin with complete recovery.

Forty-two patients underwent suprapubic operations on the bladder, with 2 deaths. Twenty-seven of the 42 patients were suffering from carcinoma of the bladder. It is interesting to note that total cystectomy for carcinoma was performed on 4 patients without a death. During 1935, 695 patients were subjected to transurethral resection of the prostate gland, whereas prostatectomy was performed on only 2. Cystostomy as a procedure preliminary to transurethral resection was performed on only 3 patients.

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[91] Priestley, J. T., and Counseller, V. S.: Review of Urologic Surgery for 1935, Proc. Staff Meet., Mayo Clin. **11**:801-804 (Dec. 16) 1936.

A total of 865 surgical procedures were performed on the external genitalia. In many instances multiple surgical procedures were performed on a single patient, especially for certain congenital anomalies which required plastic repair. The surgical treatment of undescended testes gives good results in the majority of cases, whereas experience with the hormonal treatment of this condition has not been so uniformly successful. Determinations of the gonadotropic substance in the urine have been of value in the treatment of patients who have testicular tumors, especially during the postoperative period. The authors trust that the ensuing year will settle some of the existing problems in this field of surgery and open new fields for further advances.

Seventy patients who had carcinoma of the bladder underwent treatment last year. Thirty-three per cent were treated by the suprapubic approach only. In 4 the urine was diverted above the bladder, in 3 by ureterosigmoidal anastomosis and in 1 by bilateral ureterostomy, followed by total cystectomy, without the death of any patient. Cabot has shown previously the simplicity of the technic used in performing bilateral ureterostomy and the low surgical risk. It should be possible, therefore, in treatment of some of the more advanced lesions, to perform bilateral ureterostomy and later total cystectomy and to follow these procedures by radium therapy.

By the methods used today, when preparing a patient for operation on the colon by means of injections of vaccines intraperitoneally, cleansing the bowel and special diets, it is possible in a greater number of cases successfully to transplant the ureters to the sigmoid colon and later to perform the radical operation of removal of the involved bladder.

Whenever a ureter is dilated and the walls are thickened by infection, ureterosigmoidal anastomosis should not be considered. In such cases cutaneous ureterostomy is the operation of choice. One other fact that militates against radical removal of the bladder and diversion of the urinary stream in many cases in which the lesion is of a high grade of malignancy is that metatasis to the regional lymph nodes has been discovered oftener than previously was suspected.

TRANSURETHRAL MANIPULATION

Thompson[92] stated that before the advent of the resectoscope the complete destruction of an epithelioma of the bladder of a diameter much greater than 1 cm. involved repeated electrocoagulation of the growth at intervals of from a week to a month. The cutting loop of the resectoscope has been found to be a satisfactory instrument for the rapid removal of many tumors of a pedunculate or relatively noninfiltrating type. The bulk of the growth can be rapidly removed with the cutting current, after which the pedicle or base can be thoroughly destroyed by electrocoagulation.

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[92] Thompson, G. J.: Transurethral Operations: Changing Conceptions During the Past Five Years, J. A. M. A. **107**:1954-1958 (Dec. 12) 1936.

In some cases, particularly in those in which microscopic study reveals a high grade of malignancy, it is well after removal of the tumor to implant radon seeds in the underlying wall of the bladder. In certain cases in which the extent of the lesion or the general condition of the patient has precluded radical surgical removal, this method, combined with subsequent roentgen therapy, has resulted in remarkable palliation, and in some instances it apparently has resulted in a cure.

At the Mayo Clinic during the period from 1932 to 1935 inclusive, tumors have been destroyed in 191 cases by the methods outlined, practically always at one sitting. The results to date from such treatment have been gratifying, on the whole, although sufficient time has not elapsed to warrant final conclusions concerning the efficacy of the method.

Litholapaxy has been advocated for many years for the removal of calculi in the urinary bladder. The presence of a considerably hypertrophied prostate gland was always deemed a contraindication to litholapaxy. Thompson has previously reported a series of cases in which he was able to crush and remove large calculi and, using the same anesthetic, to resect the obstructing portion of the prostate gland. The greatest amount of tissue removed in any case was 47 Gm. It is important that litholapaxy be performed rapidly; hence a lithotrite of the Bigelow type is used by preference. As a general rule it is best to crush the stone prior to prostatic resection, but if the lithotrite cannot be passed easily beyond the prostatic enlargement, it may be necessary to perform prostatic resection first. During the past four years 161 patients with vesical calculi have been treated by conservative transurethral methods at the Mayo Clinic.

Bumpus and Thompson in 1930 reported on a clinical study of 1,001 cases of ureteral calculi; in 60.7 per cent of cases in which a calculus occurred in the lower part of the ureter it was removed by transurethral methods. In most of the cases in that series more than one attempt was made before the stone was obtained, and many times it was not passed until a number of days subsequent to manipulation. During the years 1932 to 1935 inclusive, stones have been removed from the ureter by transurethral methods in 180 cases at the Mayo Clinic; in the large majority of cases the first attempt was successful, the calculus being removed at the time of the operation, either by engagement with an extractor or by the safer method of enmeshing it with multiple catheters. An attempt to force an extractor into a small ureter may result in perforation and certainly will cause severe reaction. One should prefer to insert two or three catheters alongside the stone and leave them in place for from forty-eight to seventy-two hours. Twisting the catheters at that time will often be more profitable than doing so immediately after they are placed.

Prostatic calculi often do not produce symptoms. Hence, Thompson has practically always disregarded their chance finding by routine roentgenographic study. However, when either for local or for focal reasons it is essential to reduce or eliminate the prostatitis which generally is found in association with prostatic calculi, it is not a difficult task to remove the stones by transurethral incision. Thompson prefers to use the Collings knife, for one can gage the depth of the incision, making it no deeper than is actually necessary to expose the nests of stones. Such operations must always be done with thorough recognition of the fact that the procedure is a minor one as far as the patient is concerned but that lack of caution on the part of the surgeon may easily result in a major complication, if not in death. In 8 cases Thompson has incised acute prostatic abscesses with the Collings knife, thus evacuating a large pocket of pus through the urethra.

There has been no mortality from any of the transurethral procedures described, except in the form of cases in which prostatic resection was performed. Of 1,987 patients subjected to transurethral resection for either benign or malignant involvement of the prostate gland during the years 1932 to 1935 inclusive, only 14 died, a mortality of 0.70 per cent.

INFECTION OF THE URINARY TRACT

Frisch [93] reported 47 cases of pyelitis due to colon bacillus in which bacteriophage was employed therapeutically, in all of which the condition had proved resistant to other methods of treatment. The lysin was injected into the renal pelvis, and in 2 children a subcutaneous injection was made also. The method of preparation and administration of the bacteriophage is described.

In 30 of the 47 cases cure was effected, and the urine was sterile after the treatment. In 6, there was improvement. In 6 cases the colon bacillus was resistant to the lysin during the treatment, and in these cases improvement did not occur. Five of the patients discontinued treatment before being cured.

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[93] Frisch, Bruno: Ueber das Phänomen der Bakteriophagie in der Urologie, Ztschr. f. urol. Chir. u. Gynäk. **42**:199-205, 1936.

Frisch considered bacteriophage a valuable adjunct to other methods of treatment.

Cook[94] stated that during recent years urologists have realized the value of a most careful bacteriologic investigation of the urine in cases in which infection is suspected. The simple Gram stain of urinary sediment, supplemented by culture of the urine, usually yields information of the greatest value in arriving at the proper diagnosis and is also of value in suggesting the best method of treatment. Repeated examinations are frequently necessary, especially in cases of coccic infection. It is emphasized that one organism may completely check the growth of another, the second organism coming into prominence only after the first has been partially or completely destroyed. The more common infections of the urinary tract, excluding tuberculosis, can be divided into two main groups, namely, those produced by a bacillus and those produced by a coccus. Cook is concerned with a third group of cases, however, in which no organisms can be found even after careful study. He referred to a group of patients who have definite urinary symptoms and who respond to the ordinary methods of treatment of infection in the urinary tract, but positive cultures of the urine are never obtained, although various degrees of pyuria are present. In these cases it is of prime importance to exclude tuberculosis. This is accomplished by the use of cystoscopy, urographic data, repeated examinations for acid-fast bacilli and inoculations of guinea-pigs with urine from the bladder and kidneys. The etiology of this group of cases in which specific organisms cannot be found is obscure. Almost invariably the disease has been present for months or even years, and local symptoms are well marked. Frequent urographic examinations suggest inflammation of long standing. Results of treatment, however, are ordinarily gratifying if renal function remains satisfactory. It may be necessary to continue treatment over a period of from six to eight weeks before improvement is noted. At the beginning treatment consists of lavage of the bladder with potassium permanganate (1 : 8,000) alternating with a solution of acetic acid (1 : 3,000) and followed by the instillation of silver iodide. The ketogenic diet is usually employed aided by acidification of the urine by the administration of ammonium nitrate or ammonium chloride in doses of 6 Gm. daily, if necessary, on the third or fourth day of the diet. Intravenous injections of neoarsphenamine are given at intervals of five days until from two to four injections have been administered. Careful search for foci, with eradication of these when present, is perhaps one of the most important factors in treatment. This includes investigation of the teeth, tonsils, prostate gland and cervix uteri. The author reported 4 illustrative cases in detail. It is emphasized that no single method of treatment has been uniformly satisfactory and that a combination of all forms of treatment considered has ordinarily yielded the best results. It seems that this group of cases represents a definite clinical entity.

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[94] Cook, E. N.: Infections of the Urinary Tract of Obscure *Etiology*, J. Urol. **36**:460-466 (Oct.) 1936.

Dillon[95] stated that foci of infection play an important part in the causation of infections of the urinary tract. In vague septic conditions more attention must be paid the urinary tract as a possible site of infection, in spite of negative results of clinical examination of the urine. Dentists should be taught to recognize more of the medical and surgical aspects of an infected alveolar process. Before condemning the patient with symptoms referable to the bladder and "clear urine" as neurotic, larger quantities of urine from the bladder should be sent to the bacteriologist with the request that the examination be made on the concentrated sediment of the entire specimen. Children should be watched more closely during the tooth-cutting age and attention given to dental care and hygiene. Also, during septic reactions the urinary tract should not be forgotten, and more exacting examinations should be made for the presence of bacteria in the clear urine.

URINARY ANTISEPTICS

Cook and Buchtel[96] in the past nine months have given mandelic acid to more than 250 patients. Early results indicated that it was effective in approximately 50 per cent of cases, but more recently, with more careful management, the percentage of good results has been greatly increased. For the most part sodium mandelate in a 10 per cent solution was used. A dose of 1 ounce (30 cc.) before each meal and at bed time was employed, and an acidifying drug, such as ammonium nitrate or ammonium chloride, was usually given. The intake of fluid was reduced to 1,200 cc. daily. In a series of 75 cases in which this drug was employed the urine became sterile in 61 cases, or 81 per cent. In attempting to obtain the desired acidity of the urine without the use of an additional acidifying drug, ammonium mandelate has been satisfactorily employed, following the suggestion of Holling and Platt. Only 1 patient in 15 required a secondary acidifying drug. In order to obtain the best results extreme care and alertness must be used in managing this form of treatment. The urinary p_H must remain below 5.5. Occasionally it will be necessary to employ dietary measures in addition to acidifying drugs in order to obtain the desired urinary p_H. In certain cases mandelic acid has been used in conjunction with a ketogenic diet with satisfactory results. To the present time this drug seems to be the most useful in treating bacillary infections and can be used in cases of gout, duodenal ulcer or diabetes mellitus with much less risk than the ketogenic diet. The authors stated that care should be utilized in administering the drug to aged patients or if renal function has been reduced, as it may cause a temporary detrimental effect on renal function. Less than 1 per cent of the patients complained of nausea or vomiting while mandelic acid was being administered. About 10 per cent complained of mild diarrhea, although occasionally the diarrhea was so severe that it was necessary to cease administration of the drug.

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[95] Dillon, J. R.: Urinary Tract Infection with "Clear Urine," California & West. Med. **45**:489-491 (Dec.) 1936.

[96] Cook, E. N., and Buchtel, H. A.: The Use of Mandelic Acid for Infections of the Urinary Tract, Proc. Staff Meet., Mayo Clin. **11**:538-540 (Aug. 19) 1936.

Cook,[97] because of certain unpleasant reactions and unsatisfactory results in the treatment of infections in the urinary tract by means of the ketogenic diet, has endeavored to find an adjunct to this method of treatment which will enhance the efficacy and alleviate the distressing complications. Fuller has demonstrated that the product necessary in the urine of patients on a ketogenic diet to render the urine bactericidal is beta-hydroxybutyric acid. Fuller suggested the use of this substance by mouth and recorded a small increase in the beta-hydroxybutyric acid content of the urine after the oral administration of 1 Gm. of this substance three times a day. This suggested the possibility of the oral, intravenous and local use of this substance as an adjunct to ketosis.

The oral administration of synthetic racemic beta-hydroxybutyric acid will definitely increase the urinary excretion of this substance when the patient to whom the drug is given is in a state of sufficient ketosis. There is no effect when the substance is given to a patient who displays little or no ketosis.

The local use of a 2 per cent solution of beta-hydroxybutyric acid buffered to a p_H of from 4.4 to 4.5 has proved beneficial in those cases in which the results with the diet have been unsuccessful or in which the patient has been unable to stand the dietary regimen. Seven of the 10 patients so treated gave negative urinary cultures. In 2 of the remaining 3 patients, symptoms were markedly relieved, while 1 patient obtained no benefit.

The sodium salt of beta-hydroxybutyric acid, when given orally, will produce an increase in urinary excretion of the acid but apparently to a less degree than oral administration of the pure acid.

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[97] Cook, E. N.: The Use of Beta-Hydroxybutyric Acid and Certain of Its Salts as an Adjunct in the Treatment of Infections of the Urinary Tract, J. Urol. **36**:289-297 (Sept.) 1936.

The calcium salt of the beta-hydroxybutyric acid was given intravenously in 3 cases. In none of these was an appreciable change noted in the urinary concentration of the acid.

Helmholz and Osterberg[98] recalled that they previously presented data to show that oxybutyric acid appears in the urine as the result of incomplete combustion of fats when only small amounts of carbohydrate are given in the diet. This so-called ketogenic diet is difficult for many patients to take. Recent work, originating with Rosenheim in England, has demonstrated that mandelic acid when taken orally escapes metabolism or conjugation in the animal organism and is excreted in the urine by the kidney in a concentration sufficient for bactericidal action, provided the p_H of the urine is lowered simultaneously. In man, after the oral ingestion of 5 Gm. of sodium mandelate in one dose, 80 per cent of the ingested mandelic acid appears in the urine within twenty-four hours, and the maximal excretion occurs approximately two hours after ingestion. When 3 Gm. of mandelic acid in the form of a 10 per cent solution of sodium salt is given four times during the day, there is a cumulative excretion of the acid as various quantities are ingested, and although diuresis may be produced, the concentration of the acid reaches a value in excess of 1 per cent. By administering ammonium chloride and mandelic acid together, the p_H of the urine can be lowered to approximately 5.0 over a period of many days, while a concentration of 1 per cent mandelic acid is maintained in the urine. These values have been shown to be most effective in sterilizing the urine. If from 0.25 to 1 per cent mandelic acid can be maintained in the urine, the acid will act bactericidally on most organisms at a p_H ranging from 5.0 to 5.7. Certain strains of Aerobacter and Pseudomonas are far more difficult to kill than is Escherichia coli.

Carroll, Lewis and Kappel[99] reported a clinical experience with 50 cases of pyuria in which mandelic acid was administered as suggested by Rosenheim. An analysis of their results shows 37 cases of infection due to the colon bacillus, including acute and chronic pyelitis, pyelonephritis, diverticulum of the bladder, nephroptosis, renal calculi, prostatic hypertrophy with retention and cystitis. In all these, the urine became microscopically clear under the treatment. In 7 cases the urine yielded positive cultures. The average number of days of treatment required to produce sterile urine was seven. Although the condition of 7 patients with coccic infections improved, the urine did not become sterile. In only 1 of 6 cases of infection due to Bacillus proteus was the urine made sterile. The proteus organism is the most resistant to elimination from the urinary tract. In 81 per cent of all cases of colon bacillus infection in which this manner of treatment was employed, the urine was sterile. The authors concluded from this survey that a urinary infection due to the colon bacillus group in which a p_H of 5.5 is maintained may be expected to clear up with the administration of mandelic acid within from four to twelve days. They further emphasized that pyuria is only a symptom and that complete urologic examination should always precede therapy with mandelic acid. The original causative factor in producing the pyuria must be recognized and treated together with the administration of the acid. Caution must be exercised in giving the proper dosage for fear of poisoning. Persons with lowered renal function should not be given mandelic acid.

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[98] Helmholz, H. F., and Osterberg, A. E.: Rate of Excretion and Bactericidal Power of Mandelic Acid in the Urine, J. A. M. A. **107**:1794-1796 (Nov. 28) 1936.

[99] Carroll, Grayson: Lewis, Bransford, and Kappel, Louis: Mandelic Acid as a Urinary Antiseptic: A Clinical Study, J. A. M. A. **107**:1796-1799 (Nov. 28) 1936.

URINARY EXTRAVASATION

Char, Shih and Yang [100] reported 30 cases of extravasation of urine from the Peiping Union Medical College Hospital. They stated that the most common cause of extravasation of urine is a urethral stricture caused by gonorrheal infection. The urethra proximal to the stricture gradually becomes dilated and weakened because of increased pressure and secondary infection. Rupture eventually occurs with escape of urine into the adjacent tissues. The next cause in order of frequency is trauma to the perineum or a fall astride a hard object. In 3 cases a stone was found in the urethra. The extravasation in these cases apparently was not caused by a stricture but by obstruction attributable to the stone. Occasionally in cases of severe phimosis of long duration, when the preputial opening has been reduced to the size of a pinpoint, extravasation may take place through ulceration of the inner surface of the prepuce. In such cases the urine will extravasate first into the penis and then into the scrotum.

The clinical picture of extravasation of urine is determined principally by the situation of the extravasation, the rapidity with which it occurs and the virulence of the invading organism. If extravasation is rapid, as in the case of a direct injury to the perineum or a fall astride a sharp object resulting in complete division of the urethra, the presenting symptoms will be sharp pain at the site of the injury, bleeding from the urethra, swelling in the perineum and inability to urinate.

Since extravasation is an urgent condition, treatment should be instituted as soon as possible. The treatment should aim to overcome uremia, to provide adequate drainage and to release the stricture or repair the injury to the urethra.

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[100] Char, G. Y.; Shih, H. E., and Yang, C. P.: Extravasation of Urine, Chinese M. J. **50**:807-820 (June) 1936.

Seven patients in this series died in the hospital, giving a mortality of 23 per cent. Two patients left the hospital against advice and died shortly afterward. If all the fatal cases were considered together, the mortality would amount to 30 per cent. Eight of the 9 fatal cases were from the group of cases of gonorrheal stricture, and in only 1 of these cases did death follow traumatic injury of the urethra. The deaths were mainly attributable to three factors: 1. The patients came late for treatment when the degree of acidosis and uremia was extreme. 2. The extravasation was extensive and complicated by infection by virulent organisms. 3. The distended urinary bladder was probably emptied too suddenly at the time of operation.

Negley[101] stated that the mortality from urinary extravasation is unbelievably high in persons after the age of 40. The duration of the disease is an important factor in determining the prognosis. The longer extravasation occurs, the more virulent is the infection and the less chance for recovery. Cystotomy, with incision and drainage, seems to be the operation of choice and carries the lowest mortality. Bisection of the scrotum seems in some way to detract from chance of recovery and to add to the mortality unless accompanied by other incisional drainage. The causes of death in order of frequency are septic toxemia, pyelonephritis and cardiac failure, and in most cases degeneration of kidneys, liver and spleen is associated. Periurethral, scrotal, penile, abdominal and phlegmonous processes may occur without urinary extravasation and may be entirely bacterial with exudate.

DIVERSION OF URINARY STREAM

Cabot[102] discussed the three common procedures for diverting the urine above the level of the bladder, namely, nephrostomy or pyelostomy, uretero-enterostomy and cutaneous ureterostomy. The general indications, technic and postoperative care for each procedure are considered.

Nephrostomy seems preferable to pyelostomy, except for temporary drainage, because it is more effective. Drainage is more complete and continuous and there is no leakage. Furthermore, displacement of the tube is more readily avoided, and if necessary nephrostomy may be utilized as a method for permanent drainage. Properly performed nephrostomy does not involve significant injury to the renal parenchyma.

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[101] Negley, J. C.: Urinary Extravasation, California & West. Med. **45**:38-41 (July) 1936.

[102] Cabot, Hugh: The Methods of Diverting Urine Above the Level of the Bladder, with Particular Reference to Problems of Technic, J. Urol. **35**:596-609 (June) 1936.

A fistula after nephrostomy is practically unknown, whereas it occurs more frequently after prolonged drainage by pyelostomy. The author discussed several different technics for performing nephrostomy and suggested that the method described by Cabot and Holland in 1932 is the most desirable. It is emphasized that in utilizing this procedure it is unnecessary to mobilize the kidney to any great extent except on its posterior surface. This technic involves insertion of an instrument, such as a uterine sound roughly curved in the shape of a U, through the pelvis and lower calix to the desired point on the cortical surface of the kidney. A linen suture is then tied around the bulbous end of the sound, which is pulled back through the pelvis. The suture is removed from the sound and secured on the end of a Malécot catheter, which has been previously cut to a taper; it is then pulled by the linen suture through the pelvis of the kidney and out the lower calix so that the tip of the catheter is accurately placed in the renal pelvis. Nephrostomy performed in this manner involves less damage to the renal parenchyma than when it is carried out by older methods which involve the insertion of curved forceps through the parenchyma. The postoperative care involves roentgenographic examination to determine the exact position of the tube in the kidney. This is best done by taking one film without injecting any medium and then taking one after moderately filling the pelvis with the desired opaque solution. The tube should not be removed for at least ten days, and if longer drainage is desired the original tube should be left in position; in general, as long as it drains satisfactorily and does not become encrusted.

Uretero-enterostomy may be indicated for a number of conditions, namely, congenital abnormalities, inoperable vesicovaginal fistula, intolerable vesical tuberculosis, intractable interstitial cystitis and cancer of the bladder. In general, the operation should be confined to those patients whose ureters are within approximately normal limits in size. Careful preoperative preparation of the intestinal tract by use of a low residue diet and cleansing enemas is of great importance. The author stated a preference for a two stage operation, with transplantation of one ureter at a time. The loop of sigmoid colon to be utilized is drawn through an incision in the peritoneum. After the completion of the anastomosis, the intestine is fixed to the peritoneum in such a way that the line of suture is extraperitonealized. The chief contraindication to the two stage operation is cancer of the bladder, in which case bilateral uretero-enterostomy may be desirable as a single operation. The portion of the ureter that is mobilized should be that which leads directly from the brim of the pelvis to the point on the intestine selected for anastomosis.

After uretero-enterostomy, the patient should be given fluids plentifully, either subcutaneously or intravenously. A rectal tube is kept constantly in place for from ten to fourteen days. Nothing is given by mouth for forty-eight hours, and then small amounts of water are given for the next several days, after which a liquid diet, without milk, is administered for a few more days. Enemas are contraindicated for at least ten days. When the patient's condition permits, the status of the kidneys should be determined by intravenous urography.

Cutaneous ureterostomy is almost exclusively reserved for cases in which the ureters are grossly abnormal. Under such circumstances the ureters are dilated and readily permit the introduction of a fairly large sized, soft rubber catheter. The most desirable point for bringing the ureter to the abdominal wall is just medial to the anterosuperior iliac spine. The ureter is exposed and mobilized through an oblique incision, the center of which lies on a line between the anterosuperior iliac spine and the umbilicus. The ureter is freed down into the pelvis for a distance sufficient to permit the lower end of the ureter to be brought into the wound and project beyond the skin for a distance of several centimeters. The ureter should also be freed well above the pelvic brim in such a way that it can be brought out through the incision in a gentle curve without any kinks. The ureter should be brought through the skin obliquely and not at a right angle, as the latter technic will tend to cause too sharp a bend in the ureter just below the abdominal wall. A soft rubber catheter of a size that fits snugly in the lumen of the ureter is inserted into the renal pelvis, and the satisfactory position of the tube is determined by complete aspiration of all the solution that is injected. The catheter is then held in position by two catgut ligatures which are placed one above the other close to the distal end of the ureter. No sutures are placed through the ureter.

Postoperative care in cases in which cutaneous ureterostomy has been performed involves roentgenographic examination to determine definitely the position of the tube in the renal pelvis. After the protruding portion of the ureter has sloughed off, leaving a pouting roset of mucous membrane on the abdominal wall, the catheter is maintained in position by heavy silk ties attached to pieces of adhesive tape placed at right angles to the wound. The renal pelvis is irrigated daily with a bland solution. Subsequently the necessity of irrigating the kidney depends on the amount of infection and dilatation that is present. There is considerable variation in the frequency with which the catheter should be changed. This may vary from several weeks to several months or more. No dogmatic rule can be made. The catheter should be changed with sufficient frequency to maintain complete and adequate drainage and to avoid encrustation of the catheter.

ANURIA

Cubitt[103] reported 2 cases of anuria and discussed the problems relating to this condition, particularly the reflex type, as exemplified by the renorenal or ureterorenal reflex when an obstruction on one side is capable of producing suppression in the contralateral kidney which is otherwise normal.

He said that the unobstructed kidney in cases of reflex anuria is enlarged and deeply congested. This refutes the hypothesis of a reflex vascular spasm or cramp, for the contralateral kidneys should then be small, pale and bloodless.

Recent studies on secretion of urine have disclosed that in the normal unobstructed kidney there is a certain intrarenal pressure acting in all directions within the capsules of the organ and tending to obliterate the tubules, thus offering a constant resistance to the production of urine. Increase of this intrarenal pressure through edema, ureteral obstruction with increased intrapelvic pressure or venous obstruction would result in a diminished output of urine.

It is possible that spasm of one ureter in response to impaction of a stone sets up afferent nervous impulses which, either by direct reflex action or by release of some hormone (epinephrine or posterior pituitary), cause vascular changes in the other kidney, an alteration in capillary permeability and an exudation of fluid into the renal parenchyma; the increased intrarenal pressure obstructs the tubules and raises the pressure of urine, opposing filtration; at the same time it causes partial obstruction to the venous outflow, so that the kidney is congested with blood.

In one of Cubitt's cases spinal anesthesia was used in addition to the administration of dextrose solution intravenously and ureteral catheterization, so that it was impossible to attribute the successful result which was obtained to any one type of treatment separately.

However, spinal anesthesia is put forward as a rational therapeutic measure worthy of trial in cases of reflex anuria. This applies whatever the etiology, since the afferent path at least must be a nervous one.

TRICHOMONAS

Allen[104] stated that vaginitis caused by Trichomonas vaginalis is one of the common gynecological diseases. High dry magnification of the fresh, unstained vaginal secretion under reduced illumination simplifies diagnosis. Later staining of the dried secretion will serve to distinguish the other common forms of vaginal infection, such as yeast infection and gonorrhea.

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[103] Cubitt, A. W.: The Problem of Anuria: A Review of Recent Work on Renal Physiology, with Reports of Two Cases, Brit. J. Surg. **24:**215-226 (Oct.) 1936.

[104] Allen, Edward: Trichomonas Vaginalis Vaginitis, Am. J. Surg. **33:** 523-528 (Sept.) 1936.

The profuse bubbly discharge which is found in this condition is also laden with various strains of streptococci. These streptococci may invade the urinary tract, Bartholin's glands and probably the deeper structures of the pelvis. In like manner, the urinary tract of the male may become infected during coitus either by the coccoid organisms or by the motile flagellates themselves, and a troublesome urethritis or prostatitis is the result. Constant reinfection of the female renders permanent cure impossible until the focus in the male has been treated.

Permanent cure of vaginitis caused by Trichomonas will depend on recognition of these possible avenues of infection. Elevation of the general resistance of the patient is important in the therapy.

STERILIZATION

Baer[105] stated that sterilization is permissible in any woman in whom pregnancy will aggravate existing disease which is not amenable to direct cure, undo previous corrective gynecological procedures or jeopardize her life. Written consent from both husband and wife should be obtained. Sterilization is urgently desirable in women with certain types of mental disease and congenital defects.

For permanent sterilization by surgical methods, tubal crushing and cornual excision are the simplest and surest of all the available methods. When surgical methods are contraindicated, permanent sterilization can be obtained by either roentgen or radium therapy. This always involves destruction of ovarian function and onset of the menopause.

Temporary sterilization by surgical methods is usually a failure. Irradiation for this purpose is unreliable and fraught with the risk of producing permanent sterilization. Contraception is the logical procedure if pregnancy is to be avoided temporarily.

Combined sterilization and therapeutic abortion are indicated in approximately 13 per cent of cases in which sterilization is necessary. Abdominal hysterotomy by a transverse fundal incision, which includes cornual excision, is the operation of choice.

Biologic methods for the attainment of sterilization are still entirely experimental. The only one that holds any hope in the future is the utilization of spermatoxins.

Hagner[106] stated that the most frequent cause of sterility in the male is inflammatory occlusion of the epididymis or vas deferens. Atrophy of the testis rarely occurs in epididymitis, especially in the type associated with gonorrhea. Traumatic epididymitis rarely leads to sterility.

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[105] Baer, J. L.: Sterilization, Am. J. Surg. **33**:513-517 (Sept.) 1936.

[106] Hagner, F. R.: The Operative Treatment of Sterility in the Male, J. A. M. A. **107**:1851-1854 (Dec. 5) 1936.

Hagner has never had a successful case after operation for sterility in which the patient has not had a history of bilateral epididymitis. There are two conditions that must be present for a successful result in sterility of this type: 1. The vas must be patulous above the point of anastomosis. 2. The globus major, or the upper portion of the body of the epididymis, must contain live spermatozoa. He has had no successful results except in cases in which silver wire was used as a suture. Hagner only briefly mentioned the steps of the operation, as these have been reported many times already and repetition is unnecessary. It is important to control all bleeding either by torsion or by pressure before the anastomosis is made. He has always done a bilateral operation, being careful not to make the incision in the vas too high up, thus giving a double chance for a cure and, in case of failure the first time, allowing for a subsequent operation.

In the 65 cases Hagner reported 77 operations were performed. In 12 cases a second operation was necessary because of initial failure. Of these 12 patients, 7 were cured by the second operation. Nearly all the operations were done by lateral anastomosis except the few rather atypical ones already mentioned. Sometimes one finds occlusion of the vas at the first incision, and by going further up the vas one is able to get above this obstruction. Unless great care is exercised to cut only into the lumen of the vas, which is recognizable by the yellowish tinge of its lining, there is likelihood of the operator carrying the incision through the entire diameter of the tube. It is important not to strip the vas deferens too close. Hagner places the first suture at the distal end of the incision in the vas, taking a good heavy bite, as this is the anchoring suture for the operation and the obstruction is below this point. The suture is then anchored firmly in the lower end of the elliptic incision of the epididymis. Two lateral sutures are then placed to take a fairly heavy bite in the epididymis and include some of the cut tubules. If only the fibrous covering of the epididymis is taken up in the suture, the cut tubules drop back when the anastomosis is made. The suture is then passed through the cut edges of the vas, just enough tissue being taken to approximate the edges. The last suture is passed in the same way through the upper end of the incision in the epididymis. It is then passed through the vas, at the upper angle of the incision, being carefully placed so as not to occlude the lumen. Hagner tests this out with a tear duct probe. The anastomosis is then complete. The instruments that he uses are iridectomy knives, scissors and artery forceps, such as those commonly used in operations on the eye.

Hagner stated that the operation, while tedious, is not dangerous to life. He always uses general anesthesia. He stated that in order to avoid the formation of scar tissue local infiltration should not be used. The operation cannot compromise the function of an organ that has already proved functionless. In no class of cures will the surgeon be rewarded by his patients with a greater warmth of gratitude.

REJUVENATION

Blum,[107] after discussion of the philosophic and physiologic aspects of old age and rejuvenation, took up the different types of operations and treatments for rejuvenation that have been put forth in the last years, since the first publication of Steinach in 1920. These included Steinach's operations and modifications, sympathicodiaphtheresis, transplantation of sexual glands and nonoperative treatment, such as diathermy, roentgen therapy, hormonal therapy and psychotherapy. Blum confined his paper to rejuvenation in the male.

Steinach's theory can be reviewed briefly as follows: The testis is composed of two parts, the spermatogenic and the hormonal. Old age is attributable to atrophy of the hormonal part of the testis. By ligation of the vas deferens, sperms are kept back, the spermatogenic epithelial cells atrophy by pressure, and the interstitial cells, the carriers of the hormonal production, hypertrophy.

Blum has used vasoligation in many hundred cases, mostly in patients suffering from prostatic obstruction. He has never been able to find any lasting rejuvenating effect that could not be attributed to other causes (relief of symptoms by relief of prostatic obstruction, etc.). Extensive experiments on animals (Romeis, 1933) never demonstrated any hypertrophy of the interstitial cells after vasoligation, so that Steinach's theory lacks real proof. The same is true for all modifications of Steinach's first described operation.

Not much better founded is Doppler's operation, which consists in a chemical sympathectomy of the blood vessels to the testis. By that means the blood flow to the testis is increased, but the effect wears off much too soon. Better results are obtainable from the transplantation of testes and, without any operation, from the injection of hormonal substances, especially androgen. The underlying thought in all treatments for rejuvenation, or as Blum would prefer to call it, reactivation and regeneration, is an increased circulation of hormones in the organism. It is essential that the hormones find an organism which is still able and ready to react to them. This increase of hormones can be reached by injection or by activation of endocrine glands by treatment with diathermy, roentgen rays and ultraviolet light. Those measures should be tried out first, and operation, with its short effect, performed only in exceptional cases.

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[107] Blum, Viktor: Verjüngung und Verjüngungsoperationen, Wien. med. Wchnschr. **86**:989-994 (Sept. 5) 1936.

UROGRAPHY

Osterberg[108] was prompted to describe the opaque medium used by the Section on Urology at the Mayo Clinic for the purpose of retrograde pyelography because of frequent inquiry as to its composition and preparation. This medium has been used for several years and has been satisfactory.

It is prepared as follows:

> Hippuran crystals, 160 Gm., are dissolved in 200 cc. of commercially prepared solution which contains metaphen, 1:2,500. This quantity is increased to 800 cc. by the addition of a solution of 6 per cent acacia and 1 per cent sodium chloride. This 6 per cent solution of acacia is the same as that used for intravenous purposes. Addition of acacia results in precipitation of a small amount of hippuran. This precipitate is filtered off on a Buchner funnel, and the clear solution is placed in 15 cc. cotton-stoppered tubes. These are autoclaved, and the medium is ready for use. If difficulty is encountered in obtaining a clear solution, filtration through a pad of infusorial earth may be resorted to. The resulting solution contains approximately 20 per cent hippuran, 4 per cent acacia and metaphen, 1:10,000, to insure self-sterilization.

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[108] Osterberg, A. E.: Preparation of Medium for Retrograde Pyelography, Proc. Staff Meet., Mayo Clin. **11**:560 (Aug. 26) 1936.

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INTERNAL FIXATION OF FRACTURES OF THE NECK OF THE FEMUR

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A fracture of the neck of the femur is a serious injury and to the aged person it is practically a death blow. Because of the teachings of two midwestern surgeons, Ruth and Maxwell, and as a result of the work of Royal Whitman, the medical profession a generation ago became aware that union could be obtained after this type of fracture in a fair proportion of cases if rational and efficient treatment was promptly instituted. Sufficient data have now been gathered to enable one to evaluate Royal Whitman's method,[1] which is almost universally used in America. A commission appointed by the American Orthopaedic Association [2] reported that bony union was secured by the Whitman method in about 50 per cent of the cases in which the patients were less than 60 years of age, but that in cases in which the patients were more than 60 there was a sharp decrease in the percentage of good results. The mortality incident to the accident and treatment varied, but the average was about 15 per cent. Furthermore, the report definitely indicated that results were better where some form of internal fixation was provided.

The reasons for such unsatisfactory results following conservative measures are many. It is not sufficient to blame the advanced age of the patient, because other fractures in an elderly person unite readily.

ANATOMIC STRUCTURE

The crux of the situation rests in the anatomic structure of the neck and head of the femur. The proximal fragment cannot be controlled because there is no way of grasping it, so the lower fragment must be brought into alinement and maintained there. If the fragments

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From the Section on Orthopedic Surgery, the Mayo Clinic.

[1] Whitman, Royal: The Abduction Method, Considered as the Exponent of a Treatment for All Forms of Fracture at the Hip in Accord with Surgical Principles, Am. J. Surg. **21**:335-344 (Sept.) 1933.

[2] Report of a Commission Appointed by the American Orthopaedic Association to Study the End Results of Intracapsular Fractures of the Neck of the Femur, J. Bone & Joint Surg. **12**:966-969 (Oct.) 1930.

are not securely held in this position, the shearing force that is produced by the pull of the powerful pelvic and femoral muscles and by the angle that the neck of the femur forms with the shaft, which is about 127 degrees, will either cause angulation at the site of fracture or cause the lower fragment to slip upward. The capsule of the hip joint may be so torn that it will lie between the fragments. This is probably a rare happening, but I have found it when the joint was opened in several cases. Gaenslen [3] recently reported a series of experiments in which fractures of the hips of dogs were produced by arthrotomy. Although the capsule was tucked in and held by sutures between the fragments, bony union was secured if the fragments were spiked together with knitting needles. His only failure to obtain union was in an animal in which he used Kirschner's wires instead of the more rigid knitting needles to provide fixation. The wires failed to maintain fixation, and Gaenslen [4] concluded that the failure to maintain fixation led to nonunion.

BLOOD SUPPLY

The blood supply may be interfered with by the trauma incident to the accident. The blood supply of the head and neck of the femur is derived from four sources: the diaphysis, the epiphysis, the ligamentum teres femoris and the periosteum. The vessels which come from the diaphysis cross the epiphysial line to enter the head of the femur. The epiphysial blood vessels enter the head of the femur, along the edge of the articular surface, close to the epiphysial junction. Two groups of epiphysial vessels are recognized: One group comes from the subtrochanteric fossa and enters the head of the femur from above; the other group comes from the region about the insertion of the articular capsule on the inferior aspect of the neck of the femur and enters the lower end of the head of the bone. Blood vessels are carried by the ligamentum teres femoris. It is probable that the blood supply derived from the ligamentum teres femoris is so meager as to be of no value in about 25 per cent of elderly persons.[5] In the new-born a free blood supply through this ligament is always present. Kolodny [6] expressed the belief that the periosteal group of vessels were important, and he satisfied himself that the portion of the neck of the femur lying within the capsule possessed a periosteum which differed little, if at all, from the periosteum of the extracapsular portion of the neck of the bone. Kolodny stated that the diaphysial, periosteal and epiphysial blood vessels were the important ones in the nutrition of the head and neck of the femur of an elderly person. Therefore, it would seem that sufficient blood is supplied to the fractured bone to ensure bony repair if proper apposition of the fragments is maintained.

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[3] Gaenslen, F. J.: Fracture of the Neck of the Femur, J. A. M. A. **107**: 105-114 (July 11) 1936.

[4] Gaenslen, F. J.: Subcutaneous Spike Fixation of Fresh Fractures of the Neck of the Femur, J. Bone & Joint Surg. **17**:739-748 (July) 1935.

[5] Wolcott, W. E.: Circulation of the Head and Neck of the Femur: Its Relation to Nonunion in Fractures of the Femoral Neck, J. A. M. A. **100**:27-33 (Jan. 7) 1933.

[6] Kolodny, Anatole: The Architecture and the Blood Supply of the Head and Neck of the Femur and Their Importance in the Pathology of Fractures of the Neck, J. Bone & Joint Surg. **7**:575-597 (July) 1925.

REDUCTION AND FIXATION

The surgeon, and particularly the inexperienced one. may have difficulty not only in reducing a fracture of the neck of the femur but in providing fixation after reduction. Manipulative reduction should always be checked by roentgenograms, which should be made in the lateral as well as in the anteroposterior position, if possible. Proper reduction and fixation are the essential factors, and failure to provide the latter has led to many poor results.

ASEPTIC NECROSIS

Aseptic necrosis frequently is blamed for the failure of the fracture to unite. Gaenslen, in advocating internal fixation in the treatment of this type of fracture, said that the cause of aseptic necrosis, which too commonly is encountered in unimpacted fractures, is mobility at the site of the fracture. Absolute immobility in any cast is impossible of attainment, and if there is any great amount of absorption at the line of fracture one can readily understand how displacement of the fragments would occur.

SELECTION OF PATIENTS

Unfortunately, every patient who has a fracture of the neck of the femur cannot endure the necessary treatment. The debilitated elderly person who perhaps is suffering from the terminal stage of a constitutional disease may not be a fit subject for the ordeal, and the extremely old and feeble person who is not suffering from any well defined constitutional disability is maintaining himself on such a narrow margin that, as stated before, the accident is nearly always his death blow. The prolonged fixation in a cast incident to the Whitman method has militated more than any other factor against the carrying out of rational treatment. If the wearing of a cast for such a long period could be avoided, or if the time could be materially shortened, any patient who has enough reserve to tolerate a major surgical procedure would be able to withstand the treatment of a fracture of the neck of the femur.

OPERATIVE TREATMENT

In the hope of shortening the period of confinement and inactivity, operative fixation has been advanced at various times, only to be abandoned because no systematic study was made of the end-results in cases in which the method was used. The poor results of a method in its developmental stage are always viewed with critical eyes and may overwhelm a sound rational procedure, which, if persistently advanced and improved, would hold its place in the surgical armamentarium. Bad news travels as fast in the surgical world as it does in other walks of life.

The Smith-Petersen Nail.—Smith-Petersen,[7] of Boston, in 1931 reported the use of a triple flanged metal nail in the treatment of fractures of the neck of the femur. The results with this method were so good that attention was promptly attracted to it. Johansson,[8] of Sweden, and King,[9] of Australia, have advocated the use of the Smith-Petersen flanged nail, but they use a cannulated nail so that it can be driven in over a guiding wire. The literature on the subject is increasing. Thomas,[10] Knowles,[11] Gaenslen,[4] Moore,[12] Wescott,[13] W. Meyer [14] and others, including myself, have reported fractures of the neck of the femur which have been treated by internal fixation and have described the technic of the method. Sufficient data have now been recorded to prove that the results with this method are quite good.

Impacted Fractures.—Too often, the surgeon has been lulled into a false sense of security in the treatment of a fracture of the neck of the femur, because the roentgenogram has dissolved what is termed "impaction" of the fragments. The impaction too frequently breaks down and, except in a rare instance, should not be trusted. The rare instance I refer to is the case in which the fracture is situated close to, or involves, the head of the femur; there is really a compression fracture of the head and the upper portion of the neck of the femur (fig. 1*a*). An impacted fracture through the middle of the neck of the femur (fig. 1*b*) or near the greater trochanter should practically always be broken up with the patient anesthetized and the fracture reduced by manipulation. Adequate fixation must then be provided in a plaster of paris cast or by aid of some form of internal fixation.

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[7] Smith-Petersen, M. N.; Cave, E. F., and Vangorder, G. W.: Intracapsular Fractures of the Neck of the Femur: Treatment of Internal Fixation, Arch. Surg. **23**:715-759 (Nov.) 1931.

[8] Johansson, Sven: On Operative Treatment of Medial Fractures of the Neck of the Femur, Acta orthop. Scandinav. **3**:362-392, 1932.

[9] King, Thomas: Recent Intracapsular Fractures of the Neck of the Femur: A Critical Consideration of Their Treatment and a Description of a New Technique, M. J. Australia **1**:5-15 (Jan. 6) 1934.

[10] Thomas, T. T.: Fixation by a Wood Screw Without Arthrotomy in Certain Fractures of the Neck of the Femur, Am. J. Surg. **35**:292-295 (Sept.) 1921.

[11] Knowles, F. L.: Fractures of the Neck of the Femur, Wisconsin M. J. **35**:106-108 (Feb.) 1936.

[12] Moore, A. T.: Fracture of the Hip Joint (Intracapsular): A New Method of Skeletal Fixation, J. South Carolina M. A. **30**:199-205 (Oct.) 1934.

[13] Wescott, H. H.: Preliminary Report of a Method of Internal Fixation of Transcervical Fractures of the Neck of the Femur in the Aged, Virginia M. Monthly **59**:197-204 (July) 1932; A Method for the Internal Fixation of Transcervical Fractures of the Femur, J. Bone & Joint Surg. **16**:372-378 (April) 1934.

[14] Meyer, W.: Result of Nailing the Head to the Neck in Intracapsular Fracture of the Left Femur, with Excellent Functional Result, Tr. New York Acad. Med. **10**:672, 1893.

Methods of Internal Fixation.—Smith-Petersen advised open reduction of the fracture and insertion of the nail by visual supervision. Reduction of the fracture by arthrotomy is truly a major operative procedure and one that should be undertaken only by experienced surgeons. With the so-called "blind" method, the fracture is reduced by one of the recognized manipulative procedures, and after roentgenographic or fluoroscopic examination reveals that reduction has been secured a small incision is made over the greater trochanter and the nail driven through the neck and well into the head of the femur. The "blind" method can be made more accurate by inserting a guiding wire after the apposition of the fragments is known to be accurate and by checking the position of the wire by anteroposterior and lateral roentgenograms. If the position of the wire is satisfactory as to direction and depth, a cannulated flanged nail is passed over it and driven through the neck and into the head of the femur. The wire is then withdrawn.

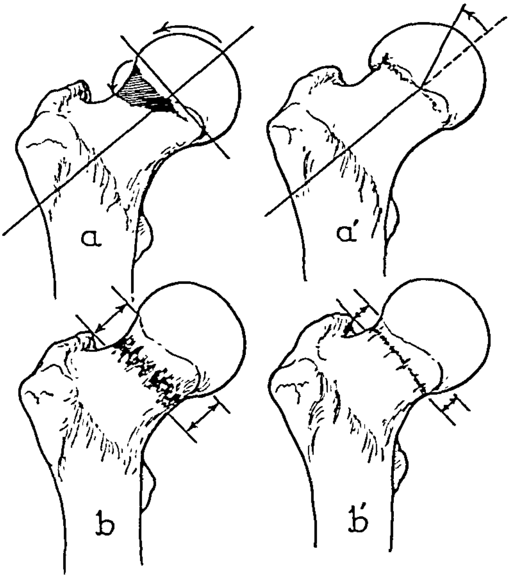

Fig. 1.—In *a* is shown a fracture of the neck of the femur, the darkened area indicating the region of compression; *a′* the position after compression; in *b*, a typical transverse fracture of the neck of the femur, the darkened area showing the region of absorption, and in *b′* union with shortening of the neck of the bone.

Insertion of the nail in this manner is not as certain to be accurate as one might expect, because even when the nail is guided by the wire it may wander and bend the wire, particularly as it enters the head of the femur. If the wire is bent to any degree, the end may break off when the wire is withdrawn through the cannulated nail. To prevent this the wire should be passed completely through the head of the femur and should extend into the acetabulum. This steadies the head of the femur as the nail crosses the line of fracture and is driven into the head of the bone. The insertion of the wire and the roentgenographic control of the position is often a prolonged procedure, for the roentgenograms have to be developed. The operation is remarkably safe if done with the patient under spinal anesthesia, for there is practically no dissection or exposure of tissue and so, no shock. I have had no experience with the reduction of such fractures under fluoroscopic control.

Objectionable Features of the Nail.—The flanged nail of Smith-Petersen is strong and in theory, at least, would seem to solve the problem of the treatment of this type of fracture. It at first was hoped it would not be necessary to apply a cast and that weight bearing could be permitted very early, but weight bearing, if permitted before bony union is well under way, has proved disastrous. It is advisable for the patient to wear a cast for from two to six weeks and permit no weight bearing for at least three months. The triple flanged nail of Smith-Petersen has a large area of metal which comes in contact with the bone, and in some instances it is poorly tolerated. Although the nail may have been driven in securely and may have been in excellent position, it may become loose as a result of absorption of bone about it and back out, as it were. How to prevent this is a problem as yet unsolved. Absorption at the line of fracture also occurs in some cases, and as the neck of the femur becomes shorter, the nail, which is firmly embedded in the head of the bone, protrudes beyond the trochanter and becomes loose.

Fixation with a Lag Screw.—Because of this difficulty, at the Mayo Clinic the use of what is called a "lag" screw has been resorted to. This will hold the fragments together. I claim nothing original for the use of the lag screw, as carpenters have long used it in cabinet work when they desired to coapt pieces of wood and it was undesirable to insert a bolt. I do not believe that it has been used previously in just this manner for the fixation of fractures of the hip, though M. O. Henry described a screw bolt similar in principle. It has been used in four cases at the clinic; in one of these cases the fracture was old, and in the others the fractures were recent. Successful results were obtained in three cases; in one case the time which has elapsed since the operation has not been sufficient to permit one to determine the end-result. The threads in the portion of the screw that goes into the head of the femur are of the wood-screw type; large and little notches are placed along the thread so that it will hold better (fig. 2). The lag screw which has been used at the clinic is cannulated and is inserted over a guiding wire.

DATA IN SIXTEEN CASES IN WHICH INTERNAL FIXATION WAS EMPLOYED

Sex and Age.—Of a group of sixteen patients with fracture of the neck of the femur who were treated with internal fixation, four were men and twelve were women. The distribution of these patients according to the various age groups follows: between 20 and 29 years, one; between 40 and 49 years, one; between 50 and 59 years, four; between 60 and 69 years, five; between 70 and 79 years, four, and between 80 and 89 years, one. Thus, ten of the patients were more than 60 years of age.

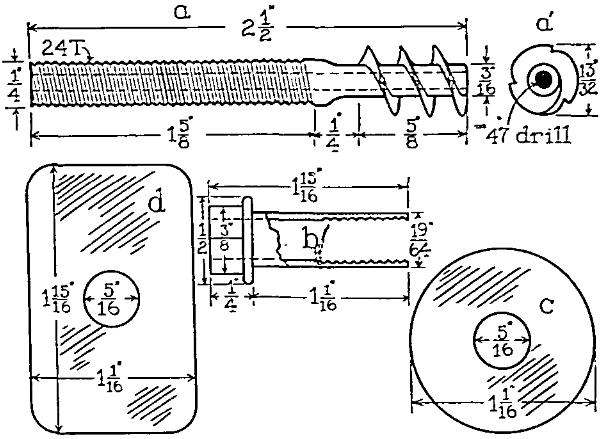

Fig. 2.—Diagram of a lag screw: *a*, the lag screw; *b*, the sleeve nut; *d* and c washers, and *a′*, the end view, showing cannulate opening.

Selection of Patients for Operation.—Any patient who was thought fit to withstand a major surgical operation was subjected to the procedure. The majority of patients were operated on as soon as the general examination was completed, and all were subjected to operation within three weeks of the accident. King, of Melbourne, Australia, prefers to make the patient comfortable and to wait three weeks before operating. By the end of that time he has a good idea as to the fitness of the patient for operation.

Anesthesia.—Spinal anesthesia is preferable; this type of anesthesia was used in eleven of the sixteen cases.

Type of Operation.—Arthrotomy was done in three cases. This permits visual supervision of the reduction of the fracture and the insertion of the nail. In the remaining thirteen cases closed reduction was done by Leadbetter's [15] method, and the nail or screw was inserted along a Kirschner wire, which was used as a guide. A cannulated Smith-Petersen nail was used in thirteen cases, a cannulated plain screw with a large thread in one case and the cannulated lag screw in two cases. The roentgenographic examination at the time of reduction showed perfect and complete reduction in nine cases. In seven cases there was overcorrection of the deformity; that is, the head of the femur was in a valgus position, which really is a desirable position, for I cannot recall that I ever have seen such a fracture overcorrected in this manner fail to unite. Preoperative classification of the fractures disclosed that one was oblique, five were transverse, and nine were impacted. All the fractures were in the neck of the femur; no trochanteric fractures are included in this series.

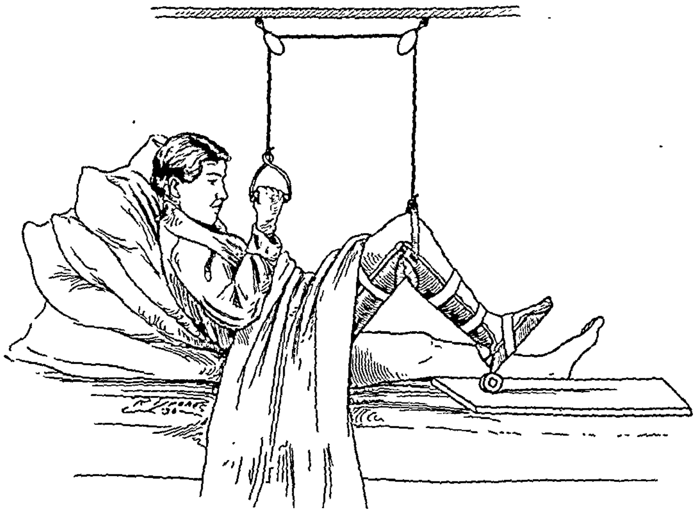

Fig. 3.—Apparatus for moving the hip.

External Fixation and Institution of Motion.—In treatment of these patients at the clinic either a single spica cast, which extended downward to the knee or a double spica, which extended from the thorax to the toes on the affected side and to the knee on the sound side, was used. The cast was bivalved or was removed in two weeks so as to permit bending of the knee, unless there was some complicating factor. Motion was instituted by aid of a sling placed under the knee, and this was pulled by the patient by means of a rope which passed through a pulley on an overhead bar (fig. 3). By this contrivance the hip is moved as the patient moves the knee.

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[15] Leadbetter, G. W.: A Treatment for Fracture of the Neck of the Femur, J. Bone & Joint Surg. **15**:931-940 (Oct.) 1933.

Weight Bearing.—The patients, on the average, were allowed up on crutches in seven weeks, and partial weight bearing was permitted. Full weight bearing without support of any kind was permitted, on the average, in four and a half months (fig. 4 *A*).

Days Spent in Hospital.—The number of days spent in the hospital averaged sixty-eight.

Removal of the Nail.—When union is complete the nail had better be removed (fig. 4 *B*). However, one patient who was past 80 years of age lived comfortably for two years with good function in spite of the fact that the nail was never removed.

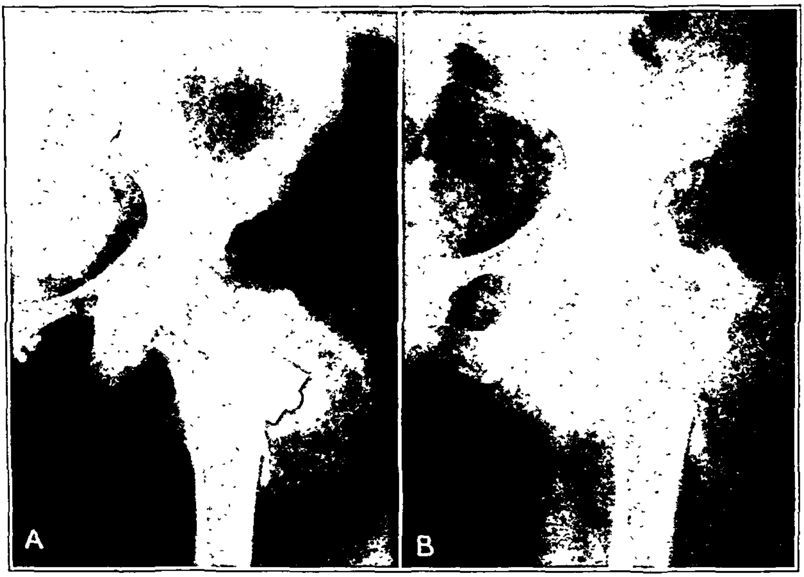

Fig. 4.—*A*, fracture of the hip united three and a half months after insertion of a lag screw. *B*, union of the fracture of the hip shown in *A*. The roentgenogram was made after removal of the lag screw.

RESULTS

There was no postoperative death or serious infection, although low grade infection developed late in two cases. Solid bony union has been secured in thirteen of the sixteen cases; one fracture definitely has failed to unite, and in two cases the results are as yet indeterminate. Therefore, of fourteen cases in which sufficient time has elapsed to be certain of the result, in thirteen, or 92.8 per cent, bony union has been obtained. In the six cases in which the patient was less than 60, the fractures united solidly. In two of the ten cases in which the patient was more than 60, the results are still indeterminate; that is, bony union is not demonstrable in the roentgenogram. I feel confident that one of these fractures will unite, but I am not so certain about the other one. In one case the result may be classified definitely as a failure. Bony union therefore occurred in seven, or 87.5 per cent, of the eight cases in which the convalescence had progressed far enough to enable one to determine the end-result.

Results of Internal Fixation in Sixteen Cases of Fracture of Neck of Femur

1. Entire group of cases	16
Deaths following operation	0
Low grade infections (late)	2
Patients still under observation	2
Cases in which nonunion occurred	1
Cases in which bony union occurred	13*
2. Patients less than 60	6
Cases in which bony union occurred	6
3. Patients more than 60	10
Cases in which nonunion occurred	1
Patients still under observation	2
Cases in which bony union occurred	7†

* This number represents 92.8 per cent of the fourteen cases in which end-results could be determined.

† This number represents 87.5 per cent of the eight cases (group 3) in which the end-results could be determined.

COMMENT

The reason for the decided interest shown in the internal fixation of fractures of the neck of the femur is that the results following the conservative treatment were on the whole unsatisfactory.

The results obtained in this limited number of cases at the clinic are far better than were ever obtained there in a similar group of cases in which the fractures were treated conservatively. The sharp pains that occur commonly after conservative reduction are absent in cases in which the fracture is treated by internal fixation, because the fixation is absolute. Many of the patients do not have the slightest pain. Furthermore, when *internal fixation* is employed the patient is much more comfortable during convalescence. The discomfort that the patient endures when he tries to limber up after he has spent three months in a cast is not encountered because early mobility of knee and hip is possible when internal fixation is employed. The effect on the morale of the patient is an exceedingly happy one. There were no deaths in the series of cases in which this type of treatment was employed at the clinic. I believe the danger of pulmonary embolism is decreased because the patients can be moved about early, active motion is permitted and the blood is kept circulating in the iliac vessels.

Pitted against these favorable aspects are an array of objections which must be considered. The insertion of the Smith-Petersen nail, the lag screw, pins or a bone graft is not easy, and the surgeon too often is chagrined and startled to find how far wrong his aim was in the insertion of these objects. This has been acknowledged by all and has led to the manufacture of many gadgets and instruments designed to overcome this difficulty. The specter of infection always hovers about these procedures. An infected hip means either death or prolonged drainage with all its discomforts, and experience with such a condition is sufficient to dampen the ardor of even the most enthusiastic surgeon. This type of operation must be done only in a properly equipped hospital and by an experienced surgeon. The nail does not always stay where it is put, for absorption about the nail may cause it to become loose and slide outward. Absorption of the neck of the femur at the site of fracture may so shorten the neck of the bone that even if the end of the nail stays in the head of the femur the head of the nail may protrude considerably beyond the trochanter and the action of the muscles during movement may further tend to loosen it. It takes at least three months for bony union to occur, and even with perfect internal fixation, full weight bearing cannot be permitted until roentgenographic examination discloses that bony union is present. While it is true that a larger percentage of patients with fractures of the neck of the femur can be treated by this method than by the Whitman method, because prolonged wearing of a cast is not necessary, if internal fixation is used indiscriminately in all cases of fracture of the neck of the femur, failures and disasters will follow and will tend to discredit the method. The incidence of fractures of the hip compared to other fractures is relatively small, so that the experience of any one man is meager unless he is in a surgical center and by agreement the patients are referred to him; therefore, the operative treatment of these fractures should be centralized and experience provided. Time will disclose whether flattening and distortion of the head of the femur are less frequent following the use of internal fixation than they are following the use of the closed method.

SUMMARY

I believe that internal fixation of fractures of the neck of the femur gives better results with no higher mortality than does conservative treatment. Therefore, internal fixation should be employed when it can be carried out in the proper surroundings and by a surgeon of sufficient training in surgical operations on the bones. Lacking such conditions, it is better either to refer the patient to a hospital where the exacting conditions can be fulfilled or to treat the patient by such conservative methods as the surgeon is familiar with. There is no hurry in carrying out internal fixation. One authority, King, of Australia, prefers to wait three weeks and thus escape the high early mortality that is encountered in conjunction with this serious injury.

CARCINOMA OF THE GALLBLADDER

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Carcinoma of the gallbladder, a rare condition in 1850, has since become a common one. The apparent increase in the incidence of the disease roughly parallels the increase in the frequency of operations on the gallbladder. The purpose of this paper is to add to the literature the data on 48 cases of carcinoma of the gallbladder observed at the New York Hospital from 1915 to 1935. After a brief historical review, the cases are analyzed pathologically, the pathogenesis being emphasized whenever possible. The same cases are then considered clinically in an attempt to clarify the clinical picture and thereby to aid in early diagnosis.

HISTORICAL REVIEW

In 1777 Maximilian Stoll,[1] of Vienna, published the first authentic record of carcinoma of the gallbladder, reporting 2 cases in which autopsy was performed. His first case not only introduced a new group of diseases but was unique, the patient having situs inversus viscerum, with carcinoma of the left-sided gallbladder. Hallé [2] in 1786 reported the next case, followed by Baillie's [3] case in 1794, the authenticity of which has been questioned.

From 1800 to 1850 but 9 cases were reported, in 2 of which the lesions probably were secondary. The first full account appeared in this period—the case of Durand-Fardel [4] in 1838.

From 1850 to 1860 9 more cases were recorded. Heschl [5] in 1852 reported 1 case and referred to 2 others which he had observed, both of which were associated with cholelithiasis.

From the Department of Surgery of the New York Hospital and Cornell Medical College.

The Department of Pathology of the New York Hospital furnished the autopsy material herein presented.

1. Stoll, Maximilian: Rations medendi, in Nosocomio practico Vindobonensi, Vienna, A. Bernardi, 1777, pt. 1, p. 290.

2. Hallé, Jean Noël: Histoire de la société de médicin, 1786 (Paris, 1790), p. 125.

3. Baillie, M.: Anatomie des krankhaften Baues von einigen der wichtigsten Theile im menschlichen Körper. Aus dem Englischen mit zusätzen von S. T. Sömmering, Berlin, Leopold Voss, 1794.

4. Durand-Fardel, C. L.: Note pour servir à l'histoire des maladies de la vésicule biliare, Bull. Soc. anat. de Paris **13**:157-160, 1838.

5. Heschl, R.: Ein Fall von Zottenkrebs der Gallenblase, Ztschr. d. k.-k. Gesellsch. d. Aerzte zu Wien **2**:251, 1852.

The decade from 1860 to 1870 enriched the literature by 15 cases. In 1870 Villard[6] collected reports of 26 cases, contributing the most complete study up to that time. Musser[7] in 1889 analyzed 100 cases; Courvoisier[8] in 1890 devoted a chapter in his "Pathologie und Chirurgie der Gallenwege" to a summary of 103 cases; Ames[9] in 1894 published his treatise, and carcinoma of the gallbladder, though uncommon, ceased to be rare.

Whereas nineteenth century writers acquainted one with the clinical and the pathologic picture of the disease, it remained for authors of the present century to emphasize its frequency. Notable contributors to the subject since 1900 are Sherrill,[10] Robson,[11] Moynihan,[12] Cotte,[13] Mayo,[14] Quenu,[15] Rolleston,[16] Smithies,[17] Fawcett and Rippmann,[18] Deaver,[19] Lentze[20] and recently Illingworth.[21] It is estimated that at least 2,000 cases have now been reported in the literature.

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[6] Villard, Ferdinand: Etude sur le cancer primitif des voies biliares, Bull. Soc. anat. de Paris **44**:217, 1869; Paris, A. Delahaye, 1870.

[7] Musser, J. H.: Primary Carcinoma of the Gallbladder and Bile Ducts, Boston M. & S. J. **121**:525-529, 1889.

[8] Courvoisier, L. G.: Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege, Leipzig, F. C. W. Vogel, 1890.

[9] Ames, D.: Primary Carcinoma of the Gall-Bladder, Bull. Johns Hopkins Hosp. **5**:74-80, 1894.

[10] Sherrill, J. G.: Cancer of the Gall-Bladder and Ducts, Ann. Surg. **44**:866-892, 1906.

[11] Robson, A. W. M.: Adenoma of the Gall-Bladder, Med.-Chir. Tr., London **88**:229-231, 1905.

[12] Moynihan, B. G. A.: Gall-Stones and Cancer, Lancet **1**:1227, 1905.

[13] Cotte, G.: Traitement chirurgicale du cancer des voies biliares, Rev. de chir. **39**:1135-1152, 1909.

[14] Mayo, W. S.: Carcinoma of the Gall-Bladder and Bile Passages, in Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, Philadelphia, W. B. Saunders Company, 1910, vol. 2, pp. 144-150.

[15] Quenu, L.: Cancer des conduits biliares, Rev. de chir. **39**:245-266, 1909.

[16] Rolleston, H. D., and McNee, J. W.: Diseases of the Liver, Gall-Bladder, and Bile-Ducts, ed. 3, New York, The Macmillan Company, 1929.

[17] Smithies, F.: Primary Carcinoma of the Gall-Bladder: An Analysis of Twenty-Three Proved Cases, Am. J. M. Sc. **157**:67-74, 1919.

[18] Fawcett, J., and Rippmann, C. H.: Carcinoma of the Gall-Bladder Associated with Gall-Stones, Guy's Hosp. Rep. **67**:41-80, 1913.

[19] Deaver, J. B.: Carcinoma of the Gall-Bladder, M. Rec. **96**:47-49, 1919.

[20] Lentze, F. A.: Gallensteine und Gallenblasenkarzinom, Beitr. z. klin. Chir. **137**:38-62, 1926.

[21] Illingworth, C. F. W.: Carcinoma of the Gallbladder, Brit. J. Surg. **23**:4-18, 1935.

INCIDENCE

This glimpse of the history of the disease fails to convey a concept of the frequency of carcinoma of the gallbladder. It probably is impossible, in the absence of compulsory necropsies, to relate its true incidence. The most reliable sources of information are large series of autopsies.

To estimate the frequency of the disease on the basis of cases in which operation was performed gives a distorted view, for these are selected. This fact may contribute to the general difference in attitude between the surgeon and the internist toward disease of the gallbladder. It certainly represents the origin of widely differing opinion concerning the frequency of carcinoma of the gallbladder. Table 1 shows the incidence of the disease in several large series of operations and autopsies. The surgical incidence, it will be noted, is more variable and several times greater than the autopsy incidence in the experience of many authors.

TABLE 1.—*Incidence of Carcinoma of the Gallbladder at Operation and Autopsy*

Author	Operations on Gallbladder	Autopsies	Carcinoma of Gallbladder	Incidence, Percentage
Erdmann: New York M. J. **111**: 705-707, 1920	224	......	15	6.70
Illingworth[21]	1,057	......	34	3.20
Smithies[17]	1,000	......	23	2.30
Deaver[10]	1,000	......	16	1.60
Judd and Gray: Surg. Gynec. & Obst. **55**: 308-315, 1932	22,365	......	212	1.00
Illingworth[21]	......	8,490	36	0.42
Fawcett and Rippmann[18]	......	592	48	0.81
von Berenscy and von Wolff: Ztschr. f. Krebsforsch. **21**: 109-118, 1924	......	19,903	300	1.50

The data in the 48 cases of the New York Hospital were compiled from surgical and autopsy material. Forty-five cases were found in a group of 1,500 operations on the gallbladder, a surgical incidence of 3 per cent. The remaining cases were not discovered at operation. Of the 2,941 autopsies performed between 1915 and 1935, 18 showed carcinoma of the gallbladder, an autopsy incidence of 0.61 per cent.

AGE AND SEX DISTRIBUTION

The age incidence of carcinoma of the gallbladder closely corresponds to that of cancer as a whole. Most cases occur in persons between the ages of 50 and 60. It is interesting to note that inflammatory disease of the gallbladder is most common in persons between 40 and 50, some ten years earlier.

The youngest patient on record is a 22 year old boy (Proescher[22]). Several cases are recorded in persons in the third decade. The oldest patient was mentioned by Illingworth[21] as being 95.

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[22] Proescher, F.: A Remarkable Case of Carcinoma of the Gallbladder in a Man Twenty-Two Years Old, J. A. M. A. **48**:481-483 (Feb. 9) 1907.

The age distribution in several groups of cases is shown in table 2. The average age in this series is 53.6 years; the youngest patient was 28 and the oldest 85.

Carcinoma of the gallbladder is more common in women than in men, the ratio being roughly 4:1. The proportion probably is due to the preponderance of cholelithiasis in women. In most series from 80 to 90 per cent of the patients are women. In this group 77 per cent were women.

ETIOLOGY

Probably there is no truer concept of the etiology of carcinoma of the gallbladder than of cancer of any other organ. Cohnheim's theory of embryonic rests has been invoked, especially to explain squamous carcinoma of the gallbladder. Some English authors have thought heredity significant. Multiple papillomas of the gallbladder have been considered precancerous. The mass of evidence on the incidence of cholelithiasis in cancer of the gallbladder established chronic irritation as a more likely predicant. Experimental studies, while inconclusive, support this theory.

TABLE 2.—*Age Distribution in Several Groups of Cases*

Years	All Cancer,* Percentage	Judd and Gray's,† Percentage	Author's Series Percentage
1- 9	0.5	....	...
10-19	0.5	....	....
20-29	1.3	0.9	2.0
30-39	4.6	4.5	4.2
40-49	12.6	14.9	25.4
50-59	21.7	40.3	31.2
60-69	27.1	33.1	20.8
70-79	23.1	6.0	4.2
80-89	7.5	....	2.0
90-99	0.6	....	....

* *United States Mortality Statistics, 1932, pp. 134-135.*
† Surg., Gynec. & Obst. **55**: 308-315, 1932.

Relation of Cholelithiasis.—In Musser's cases of carcinoma of the gallbladder the incidence of cholelithiasis was 69 per cent; Janowski's[23] series represented the other extreme, with an incidence of 100 per cent. In the 890 cases reviewed by Lentze[20] in 1926, the incidence of cholelithiasis was 83 per cent. In the remaining 17 per cent, carcinoma was superimposed on inflammatory lesions. In the present series the incidence of cholelithiasis was 79 per cent. Lancereaux[24] and others expressed the belief that stones are formed secondary to carcinoma. The weight of evidence is contrary to this view. In 48 per cent of the cases at the New York Hospital there was a history of colic of long duration.

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[23] Janowski, W.: Ueber Veränderungen in der Gallenblase beim Vorhandensein von Gallensteinen, Beitr. z. path. Anat. u. z. allg. Path. **10**:449-480, 1891.

[24] Lancereaux, M.: Du cancer de la vésicule biliare, Semaine méd. 7:334, 1887.

and many of the stones were of the calcified type, which are known to form slowly. Furthermore, Graham[25] collected reports of 38 cases of metastatic carcinoma of the gallbladder in which the incidence of cholelithiasis was only 8 per cent, a figure which approaches the incidence of simple cholelithiasis for this age group. Such observations are prima facie evidence that cholelithiasis predisposes to carcinoma of the gallbladder.

Kazama[26] in 1922 was the first to test this relation experimentally. He inserted foreign bodies (stones, sutures and mucosa) into the gallbladders of guinea-pigs and found that after a time carcinoma of the gallbladder, even a metastasizing tumor, developed in some of the animals. His researches stimulated a series of similar experiments by Leitsch,[27] Clemente[28] and others, the results of which are controversial. Lazarus-Barlow,[29] who demonstrated radio-activity in the salts of some gallstones, suggested that this radiation caused the malignant growth.

Burrows[30] recently reviewed the subject of the experimental production of carcinoma of the gallbladder. After cautious study, he concluded that cancer has not been produced and that the numerous attempts have failed to demonstrate any carcinogenic substance in gallstones. Foreign bodies in the gallbladder stimulate proliferative reactions in the mucosa that simulate cancer but do not cross the indefinite boundary between metaplasia and neoplasia.

Relation of Infection.—A pathologic change more constant than cholelithiasis is infection. In cases of carcinoma in the early stage in which only a small portion of the mucosa is invaded by tumor, there are always varying degrees of subacute or chronic infection with fibrous thickening of the free portion of the organ, depicting a long-standing inflammatory process. Consequently, all recent observers have accepted infection as a precursor of carcinoma.

Relation of Papillomas.—In 1910 MacCarty[31] emphasized the frequency of benign papillomas of the gallbladder, describing the con-

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25. Graham, E. A.: The Prevention of Carcinoma of the Gallbladder, Ann. Surg. **93**:317-322, 1931.

26. Kazama, Y.: The Studies on the Artificial Production of Tumors in the Viscera, Japan M. World **2**:309-312, 1922.

27. Leitsch, A.: Gallstones and Cancer of the Gall-Bladder, Brit. M. J. **2**: 451-454, 1924.

28. Clemente, G.: Tumori sperimentali della colecisti da catrame, Arch. ital. di chir. **17**:613, 1927.

29. Lazarus-Barlow, W. S.: An Attempt at the Experimental Production of Cancer by Means of Radium, Proc. Roy. Soc. Med. (Sect. Path.) **11**:1, 1917.

30. Burrows, H.: An Experimental Inquiry into the Association Between Gallstones and Primary Cancer of the Gallbladder, Brit. J. Surg. **20**:607-629, 1933.

31. MacCarty, W. C.: Pathology of the Gallbladder and Some Associated Lesions, Ann. Surg. **51**:651-669, 1910.

dition as "cholecystitis catarrhalis papillomatosa." He considered this a type of "strawberry gallbladder," since many of the papillomas contained deposits of cholesterol. This condition has received further recognition from Mayo,[32] Keene,[33] Mölle [34] and Abell.[35]

Malignant degeneration in papillomas has been reported by Ringel,[36] Pels-Leusden [37] and others. Illingworth [21] thought that papillomas rarely show precancerous changes. Phillips,[38] in a series of 500 cases, found but 1 with carcinoma. In this case the papillomas were multiple and all benign, while the carcinoma was solitary and malignant throughout. He could not, then, prove the pathogenesis to be malignant degeneration.

The lesion described by MacCarty occurs relatively early in the course of disease of the gallbladder. All such cases show some infection in the mucosa. Stones were present in 26.8 per cent of Phillips' cases. Because of the deposits of cholesterol, it is likely that many more eventually would have formed stones. The presence of papillomas is ample evidence of the epithelial proliferative power. One cannot, then, deny that the papillomatous gallbladder has the capacity of forming carcinoma, for infection, stones and the power to proliferate are the most common etiologic factors. All that one can require further than this is the ultimate—a susceptible subject.

PATHOLOGIC PICTURE

The pathologic picture of carcinoma of the gallbladder has been described adequately by Courvoisier,[8] Kaufmann,[39] Ewing [40] and others. Pathologically, the disease may be divided into two groups: adenocarcinoma and squamous carcinoma. The adenocarcinomas may be

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32. Mayo, C. H.: Papillomas of the Gall-Bladder, in Collected Papers of the Mayo Clinic, Philladelphia, W. B. Saunders Company, 1915, vol. 7, pp. 249-255.

33. Keene, F. E.: Papilloma of the Gall-Bladder, Proc. Path. Soc., Philadelphia **38**:7, 1918.

34. Mölle, H.: Ueber Papillome der Gallenblase, nebst Mitteilung eines selbst beobachteten Falles, Beitr. z. klin. Chir. **99**:173-185, 1916.

35. Abell, I.: Papilloma and Adenoma of the Gallbladder, Ann. Surg. **77**: 276-280, 1923.

36. Ringel: Ueber Papillom der Gallenblase, Arch. f. klin. Chir. **59**:161-166, 1899.

37. Pels-Leusden, F.: Ueber papilläre Wucherungen in der *Gallenblase und ihre Beziehungen zur Cholelithiase und zum* Carcinom, Arch. f. klin. Chir. **80**:128-160, 1906.

38. Phillips, J. R.: Papilloma of the Gallbladder, Am. J. Surg. **21**:38-42, 1933.

39. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, ed. 5, Berlin, G. Reimer, 1909, vol. 5.

40. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1931, pp. 736-740.

subdivided into (*a*) papillary adenocarcinoma, (*b*) infiltrating adenocarcinoma, (*c*) scirrhous adenocarcinoma and (*d*) mucous adenocarcinoma.

Inflammation coupled with the chronic mechanical irritation caused by gallstones produces a variety of reactions in the tissues of the gallbladder. The type of reaction probably determines the type of tumor which is to form. If the submucosa is more responsive to irritation than the mucosa, the resulting papilloma may be composed chiefly of connective tissue elements covered with normal epithelium. In my opinion, this type of papilloma is the least likely to form carcinoma, for the epithelium shows growth restraint under stimulation.

Should the response be an overgrowth of epithelium, simple benign papillomas may develop. With all growth restraint removed and anaplasia in abeyance, the gallbladder may become distended with a bulky, benign papillary growth. Such rare tumors have been described by Sand and Mayer [41] and by Chappet.[42] They are clinically malignant because of their situation but are pathologically benign. Devic and Gallavardin [43] described a case in which the growth extended down into the common duct. In one of the cases in the present series the tumor was definitely of this type, though sufficient connective tissue was present to give it a villous appearance not unlike a bunch of white grapes.

ADENOCARCINOMA

Papillary Adenocarcinoma.—If anaplasia is present, the papillary overgrowth of epithelium is malignant, resulting in papillary adenocarcinoma of the gallbladder. This is a common type; in 12 per cent of the cases at the New York Hospital the condition is of this nature. The tumor is composed of multiple papillary stalks of connective tissue covered with atypical cylindric cells and infiltrated by secondary alveoli lined with cuboidal cells. The tumor may be bulky, sometimes distending the gallbladder or obstructing the cystic duct. Ulceration may limit its growth into the lumen. In general, this type of tumor is slower growing, less malignant and more bulky than any other. Infiltration is slight, metastases are late and infection is marked. Operation is performed in a good many cases for acute or subacute cholecystitis.

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41. Sand, R., and Mayer, L.: Transformation de la vésicule biliare tout entière en un kyste papillafère, Arch. de méd. expér. et d'anat. path. **23**:523-528, 1911.

42. Chappet, V.: Cancer épithélial primitif du canal cholédoque; hydropisie de la vésicule; ictère par rétention; absence de généralisation; cachexie progressive, Lyon méd. **76**:145-157, 1894.

43. Devic and Gallavardin, L.: Etude sur le cancer primitif des canaux biliaires, cholédoque, hépatique et cystique, Rev. de méd. **21**:557, 1901.

Infiltrating Adenocarcinoma.—If anaplasia is marked and ulceration present from the start, papillary overgrowth may never have a chance to occur. The result is infiltrating adenocarcinoma, which formed 56 per cent of this series. The tumor consists of infiltrating atypical alveoli and pseudo-alveoli and does not increase the bulk of the organ. It rapidly invades all layers of the gallbladder and the liver and through adhesions, the duodenum, stomach, colon, omentum and peritoneum. Metastases occur early to the regional nodes and liver. It is in this group that metastases occasionally give rise to the first clinical manifestations of disease.

Scirrhous Adenocarcinoma.—This tumor also is of the infiltrating type of adenocarcinoma, the difference being the extensive growth of new cellular connective tissue. Whether this desmoplastic quality is reaction to preexisting inflammation or to the growth of the tumor is disputed. The picture is that of extensive fibrosis infiltrated by strands of atypical epithelial cells which tend to form alveoli. The fibrosis can be considered a defense reaction or evidence of immunity to the cancerous growth which never quite succeeds in strangulating the malignant cells. Like fibrous tissue elsewhere, it contracts with age, often resulting in obliteration of the cavity of the gallbladder. It may produce an hour-glass deformity of the organ or squeeze stones into the common duct. The only remnant of the gallbladder may be a solid knot of scar tissue with a central calculus on the inferior surface of the liver. Should the tumor arise at the neck it may cause obstruction of the cystic duct and also empyema or mucocele of the gallbladder. In 25 per cent of the cases in the present series the growth was a scirrhous adenocarcinoma.

Mucous Adenocarcinoma.—In any of the three types mentioned, mucous degeneration may occur in one part or all of the tumor. It is a regressive change due to overgrowth of the mucous constituents of the gallbladder. Should mucous degeneration be a primary feature of the tumor, there may result extensive secretion of mucus and a bulky gelatinous mass which distends the gallbladder. Because of the friability of this tumor, there is a tendency to early perforation of the organ and extension of the lesion to the peritoneum. Twelve per cent of the cases in the present series showed isolated foci of mucous degeneration. There were 2 cases of bulky mucous adenocarcinoma.

SQUAMOUS CELL CARCINOMA

Neither during its development from the primitive gut nor in the adult form is there a vestige of squamous epithelium in the gallbladder. The occurrence of definite squamous cell carcinoma must, then, be the result of metaplasia. This belief is borne out by the occasional presence in the mucosa of the gallbladder of local or general leukoplakia. Lubarsch[44] found a squamous cell papilloma the size of a bean. Further irritation may initiate malignant changes. A portion or all of the tumor may have squamous characteristics. Deetz[45] reported pearl formation, but keratinization is not a marked feature.[46] The gross picture is not unlike that of scirrhous adenocarcinoma. Metastases may have the same squamous characteristics or may revert to the adenocarcinomatous type. The clinical course is like that of the scirrhous or infiltrating types. It is the least common type of carcinoma of the gallbladder. But 1 example was seen in the cases at the New York Hospital.

SITE OF ORIGIN

Carcinoma may occur in any portion of the epithelium of the gallbladder. In the majority of cases (56 per cent in the present series) the growth is so extensive that it is impossible accurately to determine the origin. Cases in which the growth is less advanced show that the tumor generally arises at the fundus or in or near the neck of the organ.

It is estimated that in from 80 to 90 per cent of the cases the growth originates in the fourth of the mucosal area represented by the dome and the neck of the gallbladder. In the remaining 10 to 20 per cent it arises at some site about the lateral walls.

The explanation of this unequal distribution harks back to the etiologic rôle of calculi. Gravity and efforts of the organ to empty itself of stones cause greater irritation to the extremities than to the walls of the organ.

In the present series, the original site of the tumor could be determined in but 21 cases. In 12 of these it was at the fundus, and in 9, at or near the neck. No discrete tumors were found on the peritoneal or hepatic walls.

Obviously, the site of the tumor may influence the course of the disease and the resulting clinical picture as much as the type of tumor. A growth may exist at the fundus and not give rise to symptoms until dissemination is advanced. A scirrhous or papillary tumor at the neck, on the contrary, may cause obstruction of the cystic duct relatively early. A tumor on the hepatic wall of the gallbladder, by its very position, is likely to extend into or metastasize to the liver earlier than one on the free peritoneal wall, while the latter may early involve adhering peritoneal organs.

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[44] Lubarsch, Otto: Pathologische Anatomie und Krebsforschung, in Arbeiten aus der pathologisch-anatomischen Abteilung des königl. hygienischen Instituts zu Posen, Wiesbaden, 1901, p. 205.

[45] Deetz, E.: Vier weitere Fälle von Plattenepithel-Krebs der Gallenblase, ein Beitrag zur Frage der Epithel-Metaplasie, Virchows Arch. f. path. Anat. **164**:381-405, 1901.

[46] Kodama, Shuichi: The Lymphatics of the Extrahepatic Biliary Passages, Surg., Gynec. & Obst. **43**:140, 1926.

MODE OF EXTENSION

From its original site in the mucosa, a carcinoma disseminates to involve the whole gallbladder and other organs. In general, this is accomplished by local extension, lymphatic metastases and blood-borne metastases.

The lymphatics of the gallbladder consist of a rich plexus of lymph channels in the subepithelial layer and a second plexus of lymph channels in the subserosal layer, which communicate by numerous short anastomotic branches, perforating the muscular layer. The subserosal plexus in turn is collected into several main lymphatic vessels, which follow the cystic artery rather closely down onto the neck of the organ, where they terminate in the cystic node ("signal gland" of Lund). From there the lymphatics extend chiefly to the chain of mesenteric nodes which lie beside the common duct and portal vein, up to the hilus of the liver. This chain of nodes also receives branches from the pancreatic nodes, the aortic nodes and the second portion of the duodenum. Kodama [46] has demonstrated a direct lymphatic connection between the gallbladder and the first portion of the duodenum in dogs. Of great importance is the original work of Poirier and Charpy [47] and of Sudler,[48] which demonstrated an intimate connection between the lymphatics of the liver and those of the subserosal layer of the gallbladder. This work is questioned by many, but it is accepted by Graham [49] and is borne out by clinical observations.

Local extension is by far the most common method of dissemination. Infiltration first takes place through the layers of the gallbladder itself, being facilitated by the cholecystic lymphatics. Because of the arrangement of the lymphatics, the infiltrating tumor tends to encase the gallbladder on all sides early, resulting in a hard, thickened organ, which is often contracted.

The liver is involved earlier and more frequently than any other organ. This is accomplished in four ways: 1. The most common route is direct extension to the adjacent right lobe of the liver faciltated by the direct connection between the hepatic lymphatics and the subserosal lymphatic plexus of the gallbladder. The process reduces the gallbladder and the adjacent portion of the liver to a hard knot of lobulated tumor tissue and seldom occurs until the gallbladder itself is completely infiltrated. Direct extension to the liver occurred in 66 per cent of the cases at the New York Hospital. 2. Hepatic metastases may occur through these same lymphatics. They usually are associated with direct extension, are multiple and small and on or near the surface of the right lobe of the liver in the region of the gallbladder. This type of metastases to the liver occurred in 36 per cent of the cases. In all of these there was also direct extension to the liver. The metastatic nodules varied in size between 2 and 6 cm. 3. Metastases to the liver may also occur through the periportal lymphatics in a retrograde fashion. In such cases there usually is metastatic involvement of the cystic and periportal nodes; the hepatic nodules are deep in the substance of the right lobe or rarely of the left lobe. In 1 case hepatic metastases of this type were present. There was gross involvement of the cystic and periportal nodes. 4. Recently Karlmark[50] concluded that hepatic metastases tend to localize in the quadrate lobe following the venous drainage of the gallbladder. His study concerns sarcoma as well as carcinoma of the gallbladder. Unquestionably the tumor occasionally may invade veins or arteries and thus give rise to bizarre blood-borne metastases to the liver or to distant organs.

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[47] Poirier, P., and Charpy, A.: Traité d'anatomie humaine, Paris, Masson & Cie, 1901, vol. 4, p. 814.

[48] Sudler, M. T.: The Architecture of the Gallbladder, Bull. Johns Hopkins Hosp. **12**:126-129, 1901.

[49] Graham, E. A.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928, pp. 30-34.

Lymphatic metastases almost invariably involve the cystic nodes (in 52 per cent of the present series) and usually the periportal nodes (in 48 per cent of the series). Beyond the periportal nodes, lymphatic metastases are not uncommonly found in the retroperitoneal nodes about the aorta and about the pancreas (in 19 per cent of the series). The involvement of the periportal and pancreatic nodes may be massive with secondary infiltration of all surrounding structures, giving rise to obstruction of the common duct or portal vein. Occasionally, the portal vein is infiltrated by neoplastic tissue, resulting in portal obstruction or rarely in fatal hemorrhage. Infection may supervene, causing local abscess formation, pylephlebitis, thrombosis of the portal vein, multiple hepatic abscesses or septicemia.

Rarely, the mediastinal, tracheobronchial or supraclavicular nodes may be involved. Cappell and Tudhope[51] reported an unusual case with cervical metastases invading the internal jugular vein upward into the sigmoid sinus and causing hemiplegia. Strangely. there were no symptoms referable to the gallbladder.

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[50] Karlmark, E.: Die Lokalisationstendenz bei Metastasierung durch die Venen in die Leber, Acta path. et microbiol. Scandinav., supp. 13, 1932, pp. 1-203.

[51] Cappell, D., and Tudhope, G.: Primary Carcinoma of the Gall-Bladder with Unusual Metastases, J. Path. & Bact. **37**:167-168, 1933.

In almost every instance there is infiltration of the peritoneum of the gallbladder, but only in the late stages of the disease is the general peritoneal cavity involved. The mucous type of tumor is most likely to result in generalized peritoneal implants, in which event ascites is common.

Involvement of the omentum is probably next in frequency. This occurs by direct extension rather than by lymphatic spread, for the omentum often is adherent to the gallbladder after inflammation.

As with acute cholecystitis, so with carcinoma, the stomach, duodenum, jejunum or colon may become adherent to the gallbladder and by virtue of contiguity may be secondarily involved by tumor. Obstructive symptoms at one of these points in the gastro-intestinal tract may mask the primary symptoms of disease of the gallbladder.

The gallbladder may perforate into a neighboring viscus, causing a cholecystic fistula. Perforation into the colon occurred in 10 per cent of Musser's [7] 100 cases, while in Riedel's [52] 77 cases there was perforation into the duodenum in 10 and into the stomach in 5. Rolleston [16] considered the formation of a fistula less common in cases of carcinoma of the gallbladder than in those of cholelithiasis. In the series of cases at New York Hospital there was but 1 case of duodenal fistula, though tumor had invaded the duodenum in 5 cases, the pylorus in 2 and the hepatic flexure in 3.

Pulmonary metastases are not uncommon; they usually are very small and near the pleura in the lower lobe of the right lung. Their occurrence at this site confirms the view that they find their way from the abdomen through the retrodiaphragmatic lymphatics. Multiple and solitary metastases to other portions of the pulmonary parenchyma occur, however, and are probably blood borne. There were pulmonary metastases in 4 per cent of the series. All were in the lower lobe of the right lung.

Distant metastases are rare, but isolated case reports show that many parts of the body may be involved by secondary tumors. Beadles [53] reported an enormous metastatic tumor of the second rib. Warthin [54] discovered a case with cutaneous pigmentation due to metastases to the adrenal glands. Osler[55] described a metastatic nodule in the breast. Wakasugi[56] found extensive metastatic involvement on the pelvic floor simulating carcinoma of the rectum. Rolleston[16] mentioned a case with metastatic tumor of the spine simulating tuberculosis.

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[52] Riedel, B.: Zur Diagnose und Therapie des Gallenblasenkarzinomes, München. med. Wchnschr. **58**:1337-1340, 1911.

[53] Beadles, C. F.: Primary Carcinoma of the Liver (Gallbladder) Associated with a Large Tumor on the Thoracic Wall, Tr. Path. Soc. London **48**:119, 1897.

[54] Warthin, A. S.: A Case of Primary Adenocarcinoma of the Gall Bladder with Secondaries in Both Adrenals, Melanosis of Skin (Addison's Disease?), Vitiligo, and Hypertrophy of the Pancreas, Philadelphia M. J. **6**:38, 82 and 120, 1900.

CLINICAL FINDINGS

Since cholecystitis and cholelithiasis so frequently precede carcinoma, the early history in many cases is typical of inflammatory disease of the gallbladder. The first complaint may antedate the symptoms for which the patient seeks relief as long as twenty or thirty years. In other cases there are no manifestations of long-standing disease, yet in many of them gallstones are found. It is known that gallstones do not invariably cause symptoms, but this is not a likely explanation of the lack of early complaints in a large percentage of patients. A more probable reason would appear to be the relative mildness of the early symptoms.

Past History.—In only 52 per cent of the cases in the present series was there a frank history of disease of the gallbladder of long standing, yet in 70 per cent of those in which no such history was elicited stones were found. The past history was typical of intermittent biliary colic in 44 per cent of the forty-eight cases and consisted of flatulent indigestion, epigastric discomfort and intolerance of fatty foods in 8 per cent. The average duration of the past symptoms was eleven and a half years. In 1 case a single attack of painless jaundice occurred three years before the patient's admission, and in another one attack of biliary colic was followed by jaundice thirty years previously. In 3 cases cholecystostomy had been performed for acute cholecystitis associated with stones. In 1 of these cases cholecystostomy was performed three times at intervals of one year, the last operation being performed two years before the present illness. In 1 case a carcinoma developed in the stump of the cystic duct four years after a cholecystectomy for cholelithiasis.

SYMPTOMS OF CARCINOMA

After the onset of carcinoma, the clinical course of cholecystitis and cholelithiasis observed in the past history is usually modified by symptoms referable to the tumor and its growth. The symptoms attributable to carcinoma of the gallbladder are pain associated with nausea, vomiting and anorexia, followed in the course of time by loss of weight and jaundice of the obstructive type. Some tenderness is usually elicited, and the gallbladder may be palpable as a hard mass in the right upper quadrant. These symptoms will be considered separately in the order of their frequency.

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[55] Osler, W.: On the Medical Aspects of Carcinoma of the Breast, Brit. M. J. **1**:1-4, 1906.

[56] Wakasugi, K.: Zur Kenntnis der sekundären Neubildungen der Tuben, Beitr. z. path. Anat. u. z. allg. Path. **47**:483, 1910.

Pain.—The most common symptom in the group of cases was pain. It occurred in 43 of the 48 cases; in 69 per cent it was the first symptom of the disease. Four of the five patients without pain at the time they were seen had had attacks of biliary colic at some earlier period. The only patient in whom pain had never been a feature had an extensive tumor, which infiltrated and obstructed the duodenum.

The pain was almost invariably referred to the epigastrium or the upper right quadrant. A woman of 28 with situs inversus viscerum had pain in the left side due to carcinoma of a left-sided gallbladder. In 2 patients pain in the right upper quadrant was the only symptom.

The pain in these patients was constant, persisting over a period of time as a dull ache, with or without exacerbations of colic. In 54 per cent it was constant and dull, with an average duration of eight weeks. An additional 46 per cent suffered colicky exacerbations.

Loss of Weight.—In 95 per cent of the 48 cases loss of weight was a prominent feature. In 5 it was clearly the first symptom, but in none was it the only symptom. The loss of weight was generally dependent on the severity of the anorexia and the gastro-intestinal disturbance. The average loss of weight was 16 pounds (7.3 Kg.); the greatest loss, 100 pounds (45.4 Kg.).

Anorexia.—This symptom was present in 85 per cent of the cases. Though often severe, it was never the outstanding feature that it is prone to be in carcinoma of the stomach.

Tenderness.—Tenderness in the right upper quadrant or over the mass was found in 73 per cent of the cases. When the tenderness was marked it was associated with more or less rigidity.

Palpable Mass.—A palpable mass was present in 50 per cent of the cases. It was described as firm and tender and varied between 6 and 10 cm. in diameter. In all cases the mass proved to be a carcinomatous gallbladder. In 2 instances the discovery by the patient himself of a mass in the right upper quadrant constituted the first manifestation of the disease.

Edge of the Liver Palpable.—The edge of the liver was palpable in 50 per cent of the cases and descended between 2 and 10 cm. below the costal margin. It could be felt in the majority of patients with jaundice, though only half of these had hepatic metastases; however, some infiltration was always present. In no instance was the liver notably nodular.

Jaundice.—This symptom was present at the time of admission in 48 per cent of the cases, and in 6 it constituted the first symptom. In 4, jaundice associated with loss of weight and anorexia was the only symptom. The average icteric index was 100 and varied between 20 and 240. The average duration of the icterus was five weeks. The jaundice usually was continuous, though in 5 cases it was intermittent, and in 2 others it fluctuated. In all instances it was due not to hepatic metastases but to obstruction of the common duct. The obstruction, in turn, was caused by pressure of metastatic nodes or infiltration by the primary tumor in 91 per cent of the cases. There were but 2 cases of choledocholithiasis. Acholic stools and bile-stained urine accompanied the jaundice in most instances. Pruritus was extremely variable.

Vomiting.—According to the recent history in 45 per cent of the cases vomiting occurred at some time. In 1 it was the first manifestation of the disease. It usually appeared in mild form related to severe pain. In 2 cases, however, it was persistent, severe and the outstanding symptom; in both of these there was duodenal obstruction due to infiltration by the tumor.

Leukocytosis.—Laboratory examination showed leukocytosis to be a variable finding, occurring in 45 per cent of the cases. The average count was 14,500 and was closely related to the extent of the associated infection.

Anemia.—Anemia was not a marked feature in this group of cases. The average hemoglobin content was 74 per cent. In 2 cases of longstanding infection in the gallbladder the readings were below 60 per cent.

Chills and Fever.—These symptoms were marked in but 2 cases; obstructive jaundice was present in both, and at autopsy cholangeitis was noted. Fever at some time during the course of the disease was of extremely common occurrence.

ATYPICAL FORMS

Rarely, patients fail to present symptoms referable to the gallbladder, the first clinical manifestations of the disease being due to metastases. In this connection Lancereaux[24] described a hepatic form of the disease characterized by belching, vague abdominal pains, enlargement of the liver and slight jaundice, the clinical course of which is essentially that of carcinoma of the liver.

The clinical picture was atypical in 7 of the cases in the present series. Four of these had symptoms of obstruction of the common duct, i. e., painless jaundice with loss of weight and anorexia. In all of these metastatic nodes were obstructing the common duct. Duodenal obstruction was the dominant feature in 2 cases, in both of which vomiting was the outstanding symptom. In 1 case there was biliary colic of short duration, with a palpable gallbladder, which is consistent with the clinical diagnosis of hydrops. At operation carcinoma was found at the fundus with a stone impacted in the cystic duct.

DIAGNOSIS

The diagnosis of carcinoma of the gallbladder is difficult to establish with certainty. With a past history of biliary colic and a recent illness characterized by steady pain, loss of weight, anorexia, obstructive jaundice and a hard palpable mass in the right upper quadrant, the diagnosis is almost certain. However, only about 30 per cent of the patients presented this combination of clinical findings.

As stated earlier, steady, dull pain in the epigastrium or the right upper quadrant proved to be the most constant symptom. The persistence of this type of pain over a period of weeks is unusual in inflammatory disease of the gallbladder. It is felt, therefore, that the type of pain is the most useful feature in differentiating carcinoma of the gallbladder and the inflammatory diseases with which it is most frequently confused. In the presence of painless jaundice, carcinoma of the common duct, ampulla of Vater or head of the pancreas must be considered. Most ampullary tumors cause occult blood in the stools, while the gallbladder is usually palpable but not tender in cancer of the head of the pancreas.

When the clinical diagnosis is uncertain, the aid of the roentgenologist usually is invoked. In spite of the recent advances in cholecystography, roentgenograms of the gallbladder seldom are of assistance in differentiating inflammatory and neoplastic diseases in this region. The reasons for this are obvious when the extent of the pathologic process in most cases of carcinoma of the gallbladder is taken into account. If sufficient normal mucosa is left to concentrate the dye and thereby render the gallbladder visible in the roentgenogram, the chances are great that calculi will obscure the picture. Often the tumor, by obstructing the cystic duct, prevents the dye from entering the gallbladder.

There are a few recent reports in the literature (notably those of Takerta,[57] Spitzenberger[58] and Albrecht[59]) which emphasize the value of the roentgenogram in diagnosing carcinoma of the gallbladder. Kirklin[60] has discussed the subject recently.

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[57] Taterka, H.: Cholezytographische Untersuchungen mittels Decholindehnung und Eigelbentlehrung, Röntgenpraxis **3**:*721-731*, 1931.

[58] Spitzenberger, O.: Zur Diagnose exulzerierender Gallenblasenkarzinome mittels des Röntgenverfahrens, Wien. klin. Wchnschr. **46**:1421-1423, 1933.

[59] Albrecht, H. V.: Die Röntgendiagnostik des Verdauungskanals, *Leipzig*, Georg Thieme, 1931.

[60] Kirklin, B. R.: Cholecystographic Diagnosis of Neoplasms of the Gallbladder, Am. J. Roentgenol. **29**:*8-16, 1933*.

In the present series of 48 cases, cholecystograms were made in only 17; in 9 of these the gallbladder could not be visualized, in 7 there were stones and in 1 the gallbladder was clearly outlined but failed to empty well. In these 17 cases, then, there was evidence of cholecystic disease, but in no instance could a diagnosis of carcinoma of the gallbladder be made by roentgen examination.

TREATMENT AND RESULTS

As in most malignant disease in which early diagnosis is difficult, the results of treatment are not encouraging. Operation was performed in 45 of the series of 48 cases, the various operations being exploratory laparotomy with removal of tissue for biopsy, cholecystectomy, cholecystostomy and gastro-enterostomy.

Exploration and biopsy of the tumor were carried out in 21 cases. In all of these obvious metastases were encountered, and the condition was therefore considered inoperable. Eight of the patients in this group succumbed to operation, a mortality of 38 per cent. In 5, death was due to bleeding in the presence of jaundice. The average duration of life after operation in the 13 survivors was three and one-half months.

Cholecystectomy was done in 16 cases. There were 4 postoperative deaths, a mortality of 25 per cent. In 2 of the fatal cases, the common duct was drained because of jaundice. Five patients presented no evidence of metastases at the time of operation. One of these 5 was known to be alive and well two years later but has since been lost from observation. The remaining 4 patients died, on an average of ten months after operation. There were 7 patients with known metastases who survived operation, but only for an average period of six months.

Cholecystostomy was performed on 6 patients. In all of these there was jaundice. Four died as the result of the operation, a mortality of 66 per cent. Three of the 4 deaths were due to hemorrhage. The 2 survivors died six weeks after operation.

Gastro-enterostomy was done on 2 patients as a palliative procedure for duodenal obstruction caused by tumorous infiltration. One patient died, and the other lived five weeks.

With possible cure in but 1 of 45 cases, the results of operation in this group are extremely poor. Not all authors report such discouraging experiences, however. Webber,[61] in grading Judd and Gray's [62] cases, mentioned 12 cases in which the patients lived over two years. Magoun and Renshaw[63] reported 7 cases in which the patients were living five years after operation. There are occasional reports in the literature of remarkable cures[64] even after resection of adjacent, infiltrated liver.[65]

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[61] Webber, I. M.: Grades of Malignancy in Primary Carcinoma of the Gallbladder, Surg., Gynec. & Obst. **44**:756-760, 1927.

[62] Judd, S. E., and Gray, H. K.: Carcinoma of the Gall-Bladder and Bile Ducts, Surg., Gynec. & Obst. **55**:308-315, 1932.

Five of the 48 patients in this series were free from metastates at the time of admission to the hospital; this confirms the contentions of Graham[25] in his excellent paper on the prevention of carcinoma of the gallbladder. He expressed the belief that the most rational attack on the disease is its prevention by removal of the gallbladder early in all cases of cholelithiasis.

Cholecystectomy has become a relatively safe procedure, and the attitude toward it is undergoing a change. Internists are more inclined to advise surgical treatment; patients are submitting to operation earlier in the course of the disease; surgeons are performing early cholecystectomy, with improved results and constantly decreasing mortality. Should this trend persist, carcinoma of the gallbladder may once more become uncommon, being confined to the cases in which the growth fails to give rise to early symptoms referable to the gallbladder.

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[63] Magoun, J., and Renshaw, K.: Malignant Neoplasm in the Gall-Bladder, Ann. Surg. **74**:700-720, 1921.

[64] Aiga, Y.: Ueber einen seltenen Fall von operativ dauernd geheilten Gallenblasenkarzinom, Zentralbl. f. Chir. **62**:212-215, 1935.

[65] Finsterer, H.: Das Karzinom der Gallenblase, Med. Klin. **28**:432-436, 1932.

PANCREATIC FISTULA

MEDICAL AND SURGICAL MANAGEMENT

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External fistula of the pancreas may be classified as either complete or incomplete. The former commonly involves the intracapitary portion of the duct of Wirsung in such manner that all the pancreatic juice is lost to the body. This event must be exceedingly rare, as the greater number of the reports encountered in the literature deal with external fistula of the incomplete variety, in which there is only a partial loss of pancreatic juice. Duodenal fistula should be differentiated, from the standpoint of classification, because that condition is complicated by the loss not only of pancreatic juice but of bile and duodenal secretion, and therefore grave and often fatal metabolic disturbances occur as a result. Furthermore, the trypsinogen of the pancreatic fluid becomes activated, and digestion of the tissues of the wound in the nearby region of the fistula rapidly ensues.

Perhaps the earliest case of pancreatic fistula recorded was that of Rommelaere in 1877.[1] Since that time numerous case reports have appeared in the literature. Fistula of the pancreas arises in various ways. It frequently follows a drainage operation on the pancreas for an acute inflammatory condition, but according to Körte,[2] it is fairly rare as a result of a stab or gun-shot wound of the abdomen. The protected anatomic location of the pancreas is the greatest safeguard against a traumatic insult of this sort,[3] but Garrè's[4] famous case of complete transverse division of the body of the pancreas with recovery, after accurate suture of the duct and parenchyma, is classic. Injury to the pancreas may follow an operation on the kidneys, spleen, stomach

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[1] Rommelaere: Observation d'une fistule pancréatique chez l'homme, Bull. Acad. roy. de méd. de Belgique **9**:1023-1042, 1877.

[2] Körte, W.: Die chirurgischen Krankheiten und der Verletzungen des Pankreas, in Billroth, T., and Luecke, G. A.: Deutsche Chirurgie, Stuttgart, F. Enke, 1898, no. 45, p. 212.

[3] Karewski, F.: Ueber isolierte subkutane Verletzungen des Pankreas und deren Behandlung, Berl. klin. Wchnschr. **44**:187-191, 1907.

[4] Garrè, C.: Totaler Querriss dess Pankreas durch Naht geheilt, Beitr. z. klin. Chir. **46**:233-340, 1905.

or duodenum.[5] In recent years several cases of pancreatic fistula have been reported after partial resection of the pancreas or excision of an islet cell tumor for the relief of hyperinsulinism.[6]

Fistula may also follow an operation for calculi of the pancreatic duct, *but probably the commonest* source is a cyst of the pancreas. It is seldom possible to extirpate such a cyst because of the difficulty of securing a satisfactory line of cleavage for dissection between the walls of the cyst and the adjacent organs, namely, the stomach, colon, great vessels and omentum. Marsupialization or drainage by tube is most often resorted to, and discharge of pancreatic juice for a variable period usually follows. Judd, Mattson and Mahorner,[7] in a report of thirty-three cases of pancreatic cyst treated by marsupialization, stated that the discharge continued for a period of from a few weeks up to two years. In none of their cases was further treatment necessary.

The recognition of uncomplicated pancreatic fistula is not difficult. Examination of the fluid for its reaction and enzyme content establishes the diagnosis. Duodenal fistula may be differentiated by the additional presence of bile and by the erosion of the margins of the wound.[8] Greater difficulty may be experienced in recognizing a pancreatic fistula when it is associated with a biliary fistula, as pointed out by Popper.[9]

The *treatment of complete external pancreatic fistula* is complicated first by the necessity of restoring pancreatic juice to the body in sufficient quantity and before serious physiologic disturbances have taken place. Hartmann and Elman[10] and McCaughan[11] have demonstrated some of the factors concerned in the mechanism of death from total pancreatic fistula in experimental animals, and McCaughan has noted the beneficial action of the daily administration of sodium chloride intravenously in prolonging the life of an animal with a fistula

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5. Mayo, W. J.: The Surgery of the Pancreas, Ann. Surg. **58:**145-150, 1913. Young, H., and Davis, David M.: Young's Practice of Urology, Philadelphia, W. B. Saunders Company, 1926, vol. 2, p. 738.

6. Whipple, A. O., and Frantz, V. K.: Adenoma of Islet Cells with Hyperinsulinism: A Review, Ann. Surg. **101:**1299-1335, 1935.

7. Judd, E. S.; Mattson, H., and Mahorner, H. R.: Pancreatic Cysts: Report of Forty-Seven Cases, Arch. Surg. **22:**838-849 (May) 1931.

8. Garis, R. W., and Merkel, W. C.: The Symptom-Complex of Complete External Pancreatic Fistula: Report of a Case, Surg., Gynec. & Obst. **59:**590-597, 1934.

9. Popper, H. L.: Pankreasfermente in der Galle, *Zentralbl. f. Chir.* **56:**2515-2517 (Oct. 5) 1929.

10. Hartmann, A. F., and Elman, R.: Effects of the Loss of Gastric and Pancreatic Secretions and Methods for Restoration of Normal Conditions in the Body, J. Exper. Med. **50:**387-405, 1929.

11. McCaughan, J. M.: Experimental Studies on the External Secretion of the Pancreas with Special Reference to the Effect of Its Complete Loss by Permanent Pancreatic Fistula, Am. J. Physiol. **97:**459-466, 1931.

of this type. Furthermore, the latter showed that pancreatic juice administered by gastric intubation could improve markedly the condition of an experimental animal practically moribund from the effects of long-continued total loss of pancreatic juice. The serious disturbance in the chemistry of the blood, viz., chlorides, carbon dioxide-combining power and the blood urea, were quickly restored to normal by this means. Cathala and Sénèque[12] were able to secure improvement in a patient with a pancreatic fistula by returning the pancreatic juice by intubation. It is interesting to note, however, that in animals death followed only in case of total fistula; when grave symptoms failed to develop, the fistula was shown subsequently to have been subtotal, and the animals frequently exhibited no untoward results whatever.

The treatment of pancreatic fistula is secondarily concerned with the attempts at closure of the fistulous tract. Conservative means should always be adopted in the beginning. The clinical investigations of Wohlgemuth[13] have laid the basis for this line of treatment, which consists in the administration of a diet low in carbohydrates and rich in alkaline foods and large doses of sodium bicarbonate. Belladonna, or rather atropine, was first recommended by Hartmann[13a] in 1924. According to others who later used atropine, the results were negligible. Wohlgemuth based his therapeutic regimen on the investigations of Pavlov,[14] who had noted that entrance of the acid gastric juice into the duodenum invariably provoked an increase in the flow of pancreatic juice. Wohlgemuth's measures were therefore designed to inhibit the rate of pancreatic secretion as much as possible. Heineke,[15] Hohmeier[16] and Schmidt[17] obtained satisfactory results by using Wohlgemuth's regimen in cases of their own. Heineke, in addition, advocated the aspiration of the fistula by means of a catheter and suction pump.

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12. Cathala, J., and Sénèque, J.: Fistula pancréatique: Réinjection du suc pancréatique; amélioration, pancréatico-gastrostomie, guérison, Presse méd. **38:** 1534-1537 (Nov. 12) 1930.

13. Wohlgemuth, J.: (*a*) Untersuchungen über den Pankreassaft des Menschen, Biochem. Ztschr. **2:**350-356, 1907; (*b*) Zur Therapie der Pankreasfistel nebst Bemerkungen über den Mechanismus der Pankrassekretion während der Verdauung, Berl. klin. Wchnschr. **45:**389-393, 1908; (*c*) Beitrag zur funktionellen Diagnostik des Pankreas, ibid. **47:**92-95, 1910.

13a. Hartmann, M., in discussion on Barthélemy, M.: Pancréatite aiguë sans stéatonécrose, Bull. et mém. Soc. nat. de chir. **50:**408, 1924.

14. Pavlov, I. P.: The Work of the Digestive Glands, translated by W. H. Thompson, ed. 2, London, C. Griffin & Co., 1910, p. 266.

15. Heineke, H.: Zur Behandlung der Pankreasfisteln, Zentralbl. f. Chir. **34:** 265-296, 1907.

16. Hohmeier, F.: Isolierte subkutane Querzerreissung des Pankreas durch Operation geheilt, München. med. Wchnschr. **54:**2036-2037, 1907.

17. Schmidt, W.: Ein Fall von Totalexstirpation einer Pankreaszyste, München med. Wchnschr. **54:**2480-2482, 1907.

Kroiss[18] recommended the administration in 50 Gm. doses, by mouth or by rectum, of a water-free product prepared by the digestion of meats and consisting largely of the amino-acids thus produced. (The specific product employed [erepton] is no longer on the market.) Ortlich[19] injected astringents and corrosives, such as tincture of iodine, silver nitrate and zinc chloride. Potter[20] applied tenth-normal hydrochloric acid to the fistulous tract by means of a dropper and between times maintained pledgets of gauze soaked in a solution of peptone in the cutaneous opening of the fistula. The use of high voltage roentgen therapy was reported as successful by Culler[21] in the cases of two soldiers with pancreatic fistula. In each case the fistula was said to have closed completely after five irradiations. Orndoff, Farrell and Ivy,[22] on the other hand, studied the effects of roentgen therapy on the pancreas in laboratory animals and concluded that while the pancreas could be temporarily injured, its power of regeneration later on overcompensated, and the total output of ferments might become even greater than normal. Our own experience in giving high voltage roentgen therapy to a patient with a pancreatic fistula and a cyst following partial pancreatectomy for hyperinsulinism (to be reported elsewhere) is in accord with the conclusions of Orndoff, Farrell and Ivy. We exposed the left upper quadrant of the abdomen to a current of 200 kilowatts and 5 milliamperes for fifteen minutes at a time, giving a total exposure of seventy-five minutes. There was no noticeable improvement, and surgical incision and drainage later became imperative.

If these conservative methods fail after trial for a reasonable period, radical measures should then be considered. The excision or extirpation of the entire fistulous tract for obvious reasons is rarely possible. In 1905 Doyen[23] reported the first instances of successful implantation of the pancreatic duct into the greater curvature of the stomach after resection of the papilla of Vater for carcinoma. Kausch[24] in 1909 reported the successful implantation of the stump of the pancreas into the duodenum after resection of a carcinoma of the papilla of Vater.

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[18] Kroiss, F.: Ein Beitrag zur Behandlung der subkutanen Duodenum-und Pankreaszerreissung, Beitr. z. klin. Chir. **76**:477-495, 1911.

[19] Ortlich, cited by Kleinschmidt.[31]

[20] Potter, C.: Treatment of Duodenal, High Intestinal and Pancreatic Fistulas, J. Missouri M. A. **29**:374-378, 1932.

[21] Culler, R. M.: Cure of Pancreatic Fistula by the Roentgen Ray, J. A. M. A. **75**:20 (July 3) 1920.

[22] Orndoff, B. H.; Farrell, J. I., and Ivy, A. C.: Studies on the Effect of Roentgen Rays on Glandular Activity: V. The Effect of Roentgen Rays on External Pancreatic Secretion, Am. J. Roentgenol. **16**:349-354, 1926.

[23] Doyen, cited by Kleinschmidt.[31]

[24] Kausch, W.: Die Resektion des mittleren Duodenum: Eine typische Operation, Zentralbl. f. Chir. **36**:1350-1376, 1909.

The experimental work of Coffey,[25] Desjardins[26] and von Fáykiss[27] on pancreatico-enterostomy was an important forward step in this difficult field of surgical technic. After the work of Doyen and Kausch on the transplantation of the pancreatic duct after resection of the papilla of Vater for carcinoma, others began to utilize the principle of this method in dealing with intractable fistula of the pancreas, particularly Jedlicka[28] (1921), Lorenz[29] (1921), Hammesfahr[30] (1923), Kleinschmidt[31] (1925), Corachan[32] (1924, Cathala and Sénèque[12] (1930) and Janes[33] (1934).

The technic consists in making a careful dissection of the fibrous fistulous tract until a sufficient length has been mobilized. This may then be implanted without tension into the nearest portion of the upper part of the gastro-intestinal tract, preferably the stomach. A tag of fat from the round ligament or the gastrocolic or gastrohepatic omentum or even a free graft of fat is stitched about the site of implantation to protect the line of suture against leakage. A small drainage tube is placed near the site of operation, and the abdominal wound is closed in the usual manner.

The entrance of pancreatic juice into the stomach seems to have no deleterious effect on gastric digestion, according to Grey[34] and Tripodi and Sherwin,[35] who investigated this problem in dogs. Ascending infection by way of the duct, even when the implantation was made into the descending portion of the colon of dogs, did not take place. In Kausch's case of pancreaticoduodenostomy for carcinoma of the papilla of Vater clinical evidence of freedom from ascending pancreatic infection is afforded. The patient died one year after operation, and the pancreas appeared to be quite normal at necropsy. The mucous membrane of the duodenum had covered the stump of the pancreas up to the opening of the duct, which was about the size of a goose-quill.

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[25] Coffey, R. C.: Pancreato-Enterostomy and Pancreatectomy, Ann. Surg. **50**: 1238-1264, 1909.

[26] Desjardins, cited by Kleinschmidt.[31]

[27] von Fáykiss, F.: Ueber experimentelle Pankreasresektion und Pankreatoenterostomie, Beitr. z. klin. Chir. **84**:188-200, 1913.

[28] Jedlicka, R.: Zur Operation der Pankreas Kysten, Zentralorg. f. d. ges. Chir. **16**:153, 1922.

[29] Lorenz, H.: Kasuistische Beiträge Zur Pankreas-und zur Gallenchirurgie, Wien. klin. Wchnschr. **34**:339-340, 1921.

[30] Hammesfahr, C.: Zur Behandlung von Pankreasfisteln, Zentralbl. f. Chir. **50**:1758-1759, 1923.

[31] Kleinschmidt, O.: Behandlung der Fisteln des Pankreas und des Ductus pancreaticus, Arch. f. klin. Chir. **135**:363-372, 1925.

[32] Corachan, M.: Sur le traitement des fistules pancréatiques, Presse méd. **36**:1394-1397 (Nov. 3) 1928.

[33] Janes, R. M.: Pancreatic Fistula: Report of a Case; Cure by Pancreato-Gastrostomy, Brit. J. Surg. **22**:296-300, 1934.

[34] Grey, E. G.: Diversion of the Pancreatic Juice, J. Exper. Med. **26**:825-839, 1917.

[35] Tripodi, A. M., and Sherwin, C. J.: Experimental Transplantation of the Pancreas into the Stomach, Arch. Surg. **28**:345-356 (Feb.) 1934.

The following is a report of a case of pancreatic fistula in which the fistula was transplanted into the stomach.

REPORT OF A CASE

A. F., a white man 49 years of age, a molder, was admitted to the Firmin Desloge Hospital on Jan. 15, 1936. He was referred to one of us (McCaughan) for the surgical closure of a pancreatic fistula, which had followed a Billroth II type of gastric resection. The history is as follows: Nine months prior to the present admission to the hospital the patient was admitted to another institution, complaining of a dull aching pain in the epigastrium of two years' duration. By January 1935 the pain, which came on rather promptly after meals, had become severe, and was accompanied by nausea and vomiting. There had been a loss of 35 pounds (15.9 Kg.) in weight during the preceding twelve months. The nonprotein nitrogen content of the blood was 85.7 mg. per hundred cubic centimeters. Roentgenographic examination of the gastro-intestinal tract at that time revealed an enormously dilated stomach with marked retention and an apparent deformity of the prepyloric segment, which was interpreted as a gastric neoplasm. On March 30 an exploratory operation was performed on the stomach, and a firm thick mass about the size of a hen's egg was found occupying the prepyloric segment of the stomach. There were no palpable lymph glands, but numerous adhesions about the pylorus, duodenum and pancreas were encountered. A posterior gastro-enterostomy was done, and resection was deferred until later because of the poor condition of the patient. On April 15, two weeks afterward, the abdomen was reopened, and the mass in the prepyloric segment of the stomach was found to have shrunk considerably in size. A partial duodenectomy and gastrectomy were done. About one third of the stomach was removed. On the fifth day after operation the patient went into moderate shock, but he rallied after a transfusion of blood. On the eighth day postoperatively a copious watery discharge came from the wound. The patient improved generally thereafter, but the discharge persisted. The flow was practically continuous, but there was a marked increase after meals and a considerable diminution during fasting and at night. On several occasions drainage ceased for periods of from one to five days, but in two such instances bits of silk suture material were extruded from the fistula, and this was followed promptly by the return of drainage. The Wohlgemuth treatment was instituted in an endeavor to bring about healing of the fistula by medical methods, but the results were unsatisfactory. At the time of entry into the Firmin Desloge Hospital the patient stated that the fistula had been draining for more than nine months.

On physical examination the patient appeared markedly undernourished. The teeth were very bad and exhibited a great many caries. Pyorrhea alveolaris was present. There were a few coarse râles in the left side of the upper part of the chest posteriorly, but otherwise the thorax was normal. There was an old median operative scar in the upper part of the abdomen, and about 4 cm. below the xyphoid process there was a tiny cutaneous opening which barely admitted the tip of a small probe. The surrounding skin appeared to be normal. A clear watery fluid was flowing profusely from this opening (fig. 1). A sample of the material was collected for study. The fluid was strongly alkaline. It had a pH of 8.56, and all three of the pancreatic enzymes could be demonstrated. A bacteriologic examination of the fluid showed gram-positive cocci in clusters and gram-negative rods which fermented lactose. These were probably contaminators from the skin, as neither fistula nor fluid presented any gross evidence of infection. The systolic blood pressure was 125 mg. of mercury and the diastolic, 94 mm. The pulse rate was 72 and the temperature 98 F. The body weight at the time of admission was 118 pounds (53.5 Kg.).

On laboratory examination the urine was normal, except for an occasional leukocyte and erythrocyte microscopically. The blood count showed 7,900 leukocytes and 3,940,000 erythrocytes; the hemoglobin content was 13 Gm. per hundred cubic centimeters. The differential count was normal. The clotting and bleeding time were both normal, as was the clot retraction time. Studies were made of the blood chemistry, with the following results: sugar, 151 mg. per hundred cubic centimeters; nonprotein nitrogen, 33 mg.; carbon dioxide content, 49 volumes per cent, and chlorides, 590 mg. A sugar tolerance test by the Shaffer-Hartmann method gave a curve within the normal zone. The Wassermann and Kahn tests of the blood were negative. Examination of the sputum gave negative results. A gastric analysis showed normal free and combined acids. Roentgenograms were taken of the chest, and a fluoroscopic examination of the stomach was made. The roentgenographic examination revealed a moderate degree of peribronchial thickening and emphysema at the bases of both lungs. The interlobular pleura on the right was thickened. A diagnosis of chronic bronchitis was made. The fluoroscopic examination showed a normal esophagus, but the stomach had been resected at its distal third. A gastro-enterostomy stoma was evident 2 inches (5 cm.) proximal to the blind end of the stomach. Barium sulfate passed freely through the stoma.

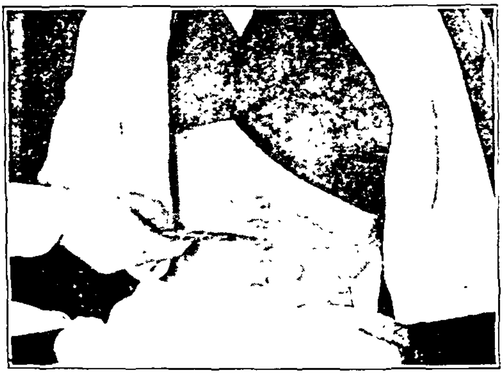

Fig. 1.—External fistula of the pancreas, indicated by the pointer.

Physiologic studies were made during the next two weeks, and the responses to various excitatory and inhibitory drugs and foodstuffs were determined. These results will be reported elsewhere. On two occasions prior to operation there was a temporary cessation of drainage, followed by headache, nausea, general malaise and an elevation of temperature to 102 F. These symptoms cleared up quickly with the return of drainage. No reason could be advanced to explain this apparent retention of pancreatic juice.

On Feb. 1, 1936, a transfusion of 600 cc. of citrated blood was given, and on February 10, with the patient under spinal anesthesia, an exploratory operation was performed on the abdomen. The incision was made at the site of the second operative scar, and a small area of skin about the fistula was left in situ. A probe was introduced into the tract as a guide, and the fistula with its attached island of

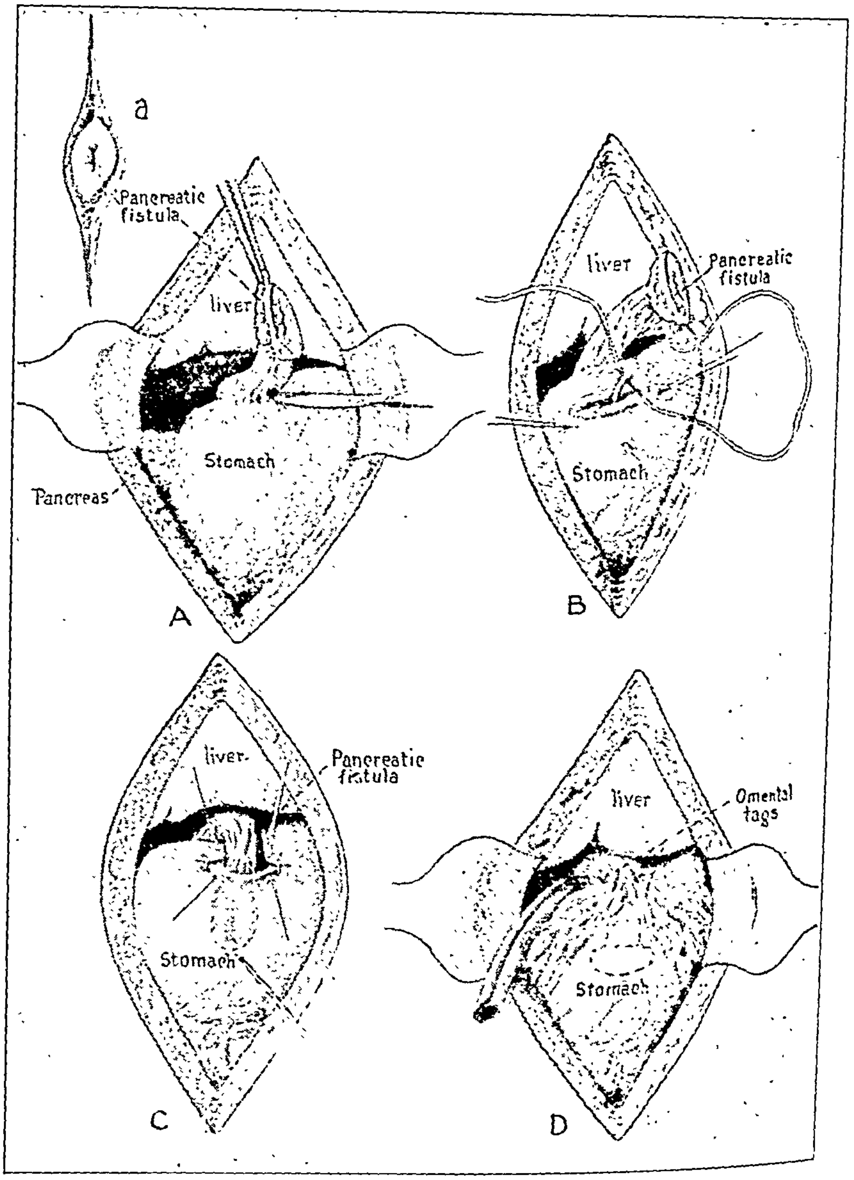

Fig. 2.—The operative technic used in the case reported here. The incision is shown in the small insert (*a*). An island of skin surrounding the opening of the fistula was left intact. In *A*, the fistula is being dissected downward. The cicatricial attachment to the lesser curvature and posterior wall of the stomach is being divided by sharp dissection, to obtain complete mobilization. The head of the pancreas is visible in the lower left side of the wound. In *B*, the stomach has been opened, and the fistula is being prepared for implantation and temporary fixation until gastric closure can be completed. In *C*, the wall of the stomach is being sutured about the fistula. In this procedure care should be taken not to constrict the tract or to produce angulation. In *D*, the omental tags of fat are shown stitched about the site of implantation, and the traction suture has been withdrawn, permitting the distal end of the fistula to hang downward. The cuff of skin prevents the fistula from slipping out. A small drain is introduced alongside the site of implantation before the abdominal closure is made.

skin was dissected free and a segment 5 cm. in length mobilized. The fistula measured approximately 1 cm. in diameter. The walls of the tract were rather thin, and some difficulty was encountered in freeing it from the lesser curvature and posterior wall of the stomach. This was accomplished by sharp dissection without injury to the stomach or to the fistula. The adhesions from the two previous laparotomies had walled off the operative field in such a manner as to separate it from the rest of the peritoneal cavity. The fistula was then implanted into the anterior wall of the stomach near the blind end. The technic employed is shown in figure 2. After operation the patient did very well until the fourth day, when a purulent expectoration and a temperature of 104 F. developed. Physical examination of the chest revealed a few moist râles. A roentgenogram showed nothing except a moderate degree of peribronchial thickening as before. These symptoms cleared up rapidly under appropriate treatment. There was considerable drainage from the wound for the first seventy-two hours. The physical and chemical characteristics of this drainage were identical with those of the fluid from the fistula which was observed previous to operation. At the same time the suture material (no. 2 chromic catgut) gave way apparently as a result of the digestive action of the escaping fluid, and the wound separated completely for a distance of about 4 cm. transversely and about 6 cm. vertically. The base of the wound was seen to be formed by the liver superiorly and the anterior wall of the stomach inferiorly and, covering both, the mesenteric fat which had been drawn up at the time of operation to protect the implanted fistula. Through and through sutures of silkworm gut above and below, however, prevented complete dehiscence. A purulent exudate appeared later, but the leakage

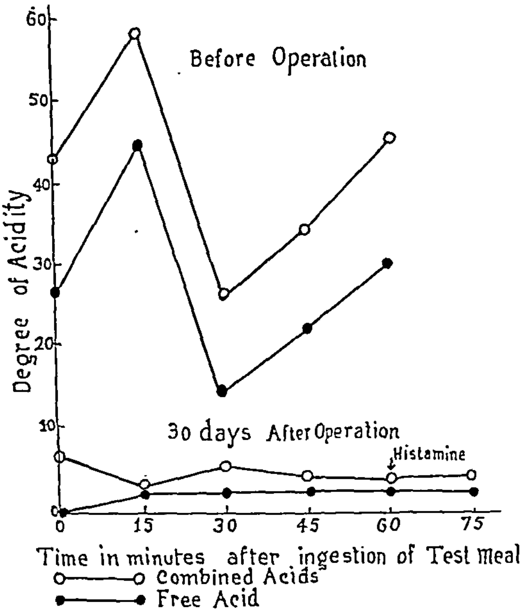

Fig. 3.—Curves showing the degree of gastric acidity before and four weeks after the implantation of the pancreatic fistula into the stomach. The test meal consisted of 240 cc. of 8 per cent ethyl alcohol given by intubation immediately after the removal of the specimen during fasting. In the postoperative analysis, 1 cc. of histamine was given after the fourth, quarter hour interval.

of pancreatic juice ceased abruptly, and with the constant application of gauze soaked in allantoin the infection cleared up gradually, and a growth of healthy granulations soon filled the defect. At the end of four weeks the wound was entirely healed except for a small crust at its center. The patient rapidly regained his weight and strength and felt much improved. Samples of the gastric fluid were also examined for lipase and were found to possess definite lipolytic activity. An index of 0.3 was found when the index for duodenal lipolytic activity by the method employed was from 1.5 to 2 units. A gastric analysis was made for comparison with that obtained before operation, and the degree of acidity was found to have fallen considerably (fig. 3). The diastase in the blood was estimated quantitatively and found to be within normal limits.

The patient was discharged from the hospital on March 15. Two months after operation we were advised that he was gaining in weight and strength. His appetite was fair. There was no dyspepsia and no diarrhea. There was no discharge from the wound, but a small herniation had developed in the lower angle of the wound. This was controlled satisfactorily with a belt.

COMMENT

A case of incomplete pancreatic fistula in which the implantation of the fistulous tract into the stomach was successful, after medical measures had failed to effect healing, is reported. The literature on pancreatic fistula is reviewed, and both conservative and radical methods of dealing with incomplete fistula are discussed in detail. It is difficult to state definitely how long medical measures should be employed before one resorts to surgical treatment. In this instance medical treatment was carried out for perhaps eight or nine months without any significant diminution in the discharge from the fistula. It is questionable whether these procedures can be depended on to bring about a continuous inhibition in the secretion of pancreatic juice. We studied the effect of a variety of drugs and food substances on the activity of pancreatic secretion in this patient, and our results will be published elsewhere. Suffice it to say here that we were able to inhibit or to excite the flow with a number of the substances given, but we question whether these effects could be effectively maintained over long periods of time. Certainly in cases in which there is a well defined fistulous tract with possibly a cicatricial stenosis proximal to it, it would appear futile to continue with the medical regimen. High voltage roentgen therapy had proved unsuccessful in a previous case (to be published elsewhere) and so was not again attempted.

The success of any surgical technic for transplantation will depend on obtaining free mobilization of the fistulous tract and its implantation without tension into the nearest available portion of the upper part of the gastro-intestinal tract, preferably the stomach. It is essential that there are no constrictions or acute angulations, since retention would thereby be favored and the development of a cyst practically a certainty. The tract should not be stitched to the wall of the stomach but should be allowed to find its own proper degree of tension exactly as in the technic for the production of a perineal urethra. If a suitable island of skin with the fistula opening at the center is left attached, the tract is not likely to slip out, and ultimately that portion beyond the site of union between the intestine and the tract may be expected to slough away as a result of autodigestion. Temporary leakage of gastric and pancreatic juice should be expected, but if the tract is patent it should cease within a few days. The final step in the operative procedure, namely, the utilization of the tags of fat from the adjacent omentum, is an important factor in minimizing the danger of permanent leakage.

The influence on gastric acidity after transplantation is of especial interest. Grey,[34] in a series of experiments, transplanted the major pancreatic duct into the wall of the stomach in dogs in which previously a Janeway fistula had been produced. Using a test meal of 70 Gm. of beef and 75 cc. of tap water, he withdrew samples from the fistula at intervals. His results in the main were in agreement with the work of Boldyreff on the self-regulation of the acidity of the stomach and illustrated a remarkable compensatory activity of the gastric glands. He found that the presence of considerable amounts of pancreatic juice in the stomach during digestion led only to a moderate decrease in the acidity level of the ingesta. After months, Grey could find no evidence of inflammatory or degenerative change in the pancreatic glands, although the patency of the ducts could be demonstrated in every instance. The marked decrease in acidity which obtained in our patient differs greatly from Grey's observation on his animals and may be the result of a difference in species. It is more likely due, however, to the fact that the principal acid-forming area of the stomach had been previously extirpated, and the remaining portion was unable to compensate in a normal manner.

In a recent review of the literature on hyperinsulinism, Whipple and his co-workers[6] reported the occurrence of pancreatic fistula in three of thirty-five cases in which operation was performed. In a similar study, we concluded that pancreatic fistula is more likely to follow the local excision of a pancreatic adenoma than partial resection of the pancreas, in which transverse division and complete removal of the distal portion are practiced. This conclusion received experimental support from the work of Korovitsky,[36] who showed that the ducts were not mere conducting tubes as some supposed, but that they possessed a definite tonus which propelled the pancreatic juice toward the duodenum.

The possibility of inadvertent and even unpreventable trauma to the pancreas during certain intra-abdominal operations should be kept in mind. Such injuries may go unrecognized at the time, but if the surgeon is aware of having injured the pancreas, there is the choice of several

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[36] Korovitsky, L. K.: The Part Played by the Ducts in Pancreatic Secretion, J. Physiol. 57:214-233, 1923.

procedures, depending, of course, on the location and extent of the wound in the pancreas. In superficial injuries the wound may be closed with a few interrupted sutures and a small drain introduced to the site of the injury before the abdomen is closed. In the case of a more extensive injury the surgeon may elect to do nothing and adopt a policy of watchful waiting with an idea of dealing with complications if and when they occur, or in cases in which the injury is located in the body or tail, he may attempt to circumvent trouble by removing the involved segment and the distal portion of the pancreas. If the major pancreatic duct were divided in the head or in the body, for example, one might attempt to resuture it, as in Garriè's classic case. Perhaps the simplest step of all with injuries situated in the body or tail would be to ligate the pancreas securely at the site of injury. The ensuing atrophy of the acinous cells proceeds rapidly without evident clinical disturbance in experimental animals in which the pancreatic ducts have been divided between ligatures. The islet tissue remains intact, and no interference with carbohydrate metabolism occurs. The digestive disturbances which follow insufficiency of the external pancreatic secretion are the result of the excessive loss of fat and nitrogen in the stools. This loss can now be fairly well controlled by the administration of certain vegetable diastases.[37] Drainage should be instituted before closure of the abdomen, in any event, particularly if nothing else can be done at the time, as the avoidance of retention and subsequent pancreatic cyst formation would seem to be especially desirable.

The likeliest sources of danger in abdominal operations are, in the order named: operations on the stomach and duodenum, operations on the biliary tract, operations on the spleen, operations on the kidneys, operations for retroperitoneal tumor and operations on the adrenal glands.

CONCLUSION

External fistula of the pancreas may be complete or incomplete. The incomplete type is the more common as well as the least serious. The treatment of incomplete pancreatic fistula is at first medical, and the basis of such management has been discussed.

The surgical treatment is indicated when conservative measures fail after a reasonable period to bring about definite and continued improvement. The surgical treatment consists in the implantation of the fistula in some readily accessible portion of the upper part of the gastrointestinal tract.

A case of an incomplete pancreatic fistula in which successful transplantation of the fistula into the stomach was done is reported in detail, and the literature is reviewed.

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[37] Whipple, A. O.; Parsons, W. B., and Mullins, C. R.: Treatment of Carcinoma of the Ampulla of Vater, Ann. Surg. **102:** 763-779, 1935.

PHYSIOLOGIC AVAILABILITY OF FLUIDS IN SECONDARY SHOCK

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The central factor in the production of traumatic shock is the reduction of the volume of blood. The exact mechanism of the oligemia occurring in shock is debatable, but at the present time most consideration has been given to three hypotheses. According to the first, vasotropic substances are formed in the area of injury and are absorbed into the general circulation, producing a marked fall in the blood pressure and an increase in the permeability of the capillaries. As a result, blood and blood plasma pass out into the extravascular tissues, and a reduction in the volume of blood takes place (Cannon,[1] Cannon and Bayliss [2] and Grunke and Haring [3]).

Subsequent observers, however, have been unable to obtain convincing evidence of the presence of such toxic products either in the area of injury (Blalock,[4] Parsons and Phemister [5] and Simonart [6]) or in the blood stream of human beings suffering from shock (Schneider [7] and Herbst [8]).

According to the second hypothesis, the reduction in the volume of blood may be satisfactorily accounted for by a loss of plasma and blood

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1. Cannon, W. B.: Experimental Traumatic Shock: Evidence of a Toxic Factor in Wound Shock, Arch. Surg. **4**:1 (Jan.) 1922.

2. Cannon, W. B., and Bayliss, W. M.: Note on Muscle Injury in Relation to Shock, Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions, Medical Research Committee, London, His Majesty's Stationery Office, 1919, p. 19.

3. Grunke, W., and Haring, W.: Das Verhalten der Blutmenge beim experimentellen Shock, Ztschr. f. d. ges. exper. Med. **79**:763, 1931.

4. Blalock, A.: Experimental Shock: Cause of Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:959 (June) 1930.

5. Parsons, E., and Phemister, D. B.: Haemorrhage and "Shock" in Traumatized Limbs: Experimental Study, Surg., Gynec. & Obst. **51**:196, 1930.

6. Simonart, A.: Etude expérimentale sur la toxémie traumatique et la toxémie des grands brûlés, Arch. internat. de pharmacodyn. et de thérap. **37**:269, 1930.

7. Schneider, H.: Ueber das Vorkommen und über die Bedeutung von Gewebsgiften bei Shockzuständen des Menschen, Deutsche Ztschr. f. Chir. **229**: 343, 1930.

8. Herbst, R.: Experimentelles zur Entstehung des traumatischen Shocks, Arch. f. klin. Chir. **176**:98, 1933.

into the traumatized region (Blalock,[4] Parsons and Phemister[5] and Herbst[6]). The basis of the third point of view is that a prolonged overactivity of the sympathetic nervous system is capable per se of reducing the volume of blood to a shock level (Freeman[9] and Malcolm[10]). This conclusion followed the observation of a diminished volume of blood in decorticate animals exhibiting sham rage and after prolonged injections of epinephrine. In both instances a hyperactivity of the sympathetic nervous system was readily demonstrable.

Whatever may be the mode of its production, the oligemia causes widespread physiologic effects, in particular an oxygen want which is directly proportional to the reduction in the volume of blood. Even a small hemorrhage and minor grade of shock induces a considerable diminution in the volume flow of blood to peripheral organs, amounting in certain instances to a decrement of as much as 80 per cent (Gesell[11]). The administration of fluid increases the flow of blood through peripheral blood vessels, even though the fluid possesses no oxygen-carrying properties. However, as will be shown later, an increased volume flow to the periphery does not result, of necessity, in an increased utilization of oxygen by anoxemic tissues.

FLUIDS IN SHOCK

In evaluating the fluid therapy of shock, two questions arise: 1. How adequate are fluids in the treatment of shock? 2. Which criteria can be considered most significant in the estimation of the depth of shock? The adequacy of a fluid in the treatment of shock must depend primarily on its ability to produce and maintain an increased volume of blood. Judged by this standard, blood is the most effective fluid available. The beneficial results obtained by the use of a 6 per cent solution of acacia (Bayliss[12]) led to its wide adoption as a therapeutic measure in cases of shock. Solution of acacia itself is incapable of transporting oxygen, but in view of the fact that in shock there is relatively little diminution of the oxygen-carrying erythrocytes in the blood stream and that concentration of the red blood cells almost invariably occurs, the use of this drug in the treatment of shock rests on a reasonable basis. Hypertonic solution of acacia and dextrose solution have been advocated

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[9] Freeman, N. E.: Decrease in Blood Volume After Prolonged Hyperactivity of Sympathetic Nervous System, Am. J. Physiol. **103**:185, 1933.

[10] Malcolm, J. D.: The Nature and Treatment of Surgical Shock, Tr. Med. Soc. London **32**:274, 1909.

[11] Gesell, R.: Studies on Submaxillary Gland: I. Dependence of Tissue Activity upon Volume-Flow of Blood and on Mechanism Controlling This Volume-Flow of Blood, Am. J. Physiol. **54**:166, 1920.

[12] Bayliss, W. M.: Intravenous Injection in Wound Shock, London, Longmans, Green & Co., 1919.

(Erlanger and Gasser[13]), but the danger of acute cardiac dilatation after their administration has prevented their general use. The ready availability of isotonic solutions of sodium chloride and dextrose solutions has made them the commonly used fluids in the treatment of shock and hemorrhage. During an investigation on the metabolic effects of water, a peculiar abnormal response was noticed in animals which had been subjected to hemorrhage (Davis[14]).

This investigation was undertaken to determine the nature and mechanism of the response of normal animals and of animals in shock to water and electrolytes. The question was raised regarding the criteria of shock to be used in this study. In view of the fact that the central phenomenon of shock is an anoxemia which is the resultant of such factors as oligemia, lowered blood pressure, diminished volume flow of blood and peripheral vasoconstriction, it was decided that the rate of oxygen consumption of the animal provided a more accurate picture of the effects of traumatic shock on the tissues. However, determinations of the blood pressure level were made to serve as controls.

METHODS

Healthy dogs weighing from 10 to 20 Kg. were used throughout these experiments. Anesthesia was induced by sodium barbital in a dosage of 250 mg. per kilogram of body weight. Surgical anesthesia was essential in order to prevent movements which might falsify the metabolism readings. The metabolic rates of several unanesthetized animals, which had been trained for such determinations, were obtained. Sodium barbital was thereafter administered in the aforementioned dosage, and only a slight depression of the rate of oxygen consumption was noticed. Moreover, the metabolism readings of trained unanesthetized animals often showed variations of from 100 to 300 cc. of oxygen consumption per ten minutes. Especially was this noticeable when readings were obtained frequently and over long periods of time. In the animals anesthetized with sodium barbital, the rate of metabolism remained remarkably constant. The metabolism determinations were made with a Krogh respiratory apparatus before and at frequent intervals during each experiment. Prior to each experiment the urinary bladder was emptied by means of a catheter, which was left in situ, in order that the urinary secretion might be measured. Fluid was administered in the form of an isotonic solution of sodium chloride (0.9 per cent) heated to 38 C. This was permitted to run into the exposed femoral vein at a constant rate of 16 cc. per minute until 3,000 cc. was given, at which point the injection was stopped. A control series of twenty normal dogs was used. In another series of fifteen animals secondary shock was produced by (1) massive hemorrhage to the extent of one third of the calculated volume of blood, (2) repeated trauma to a hindlimb, (3) ligation of the portal vein and (4) the injection of histamine dihydrochloride.

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[13] Erlanger, J., and Gasser, H. S.: Hypertonic Gum Acacia and Glucose in the Treatment of Secondary Traumatic Shock, Ann. Surg. **69**:389, 1919.

[14] Davis, H. A.: The Relation of Water and Electrolytes to Metabolism, Science **81**:493, 1935.

The blood pressure was recorded in the usual manner in the majority of these experiments.

Death following ligation of the portal vein has been ascribed to shock resulting from loss of blood and plasma into the wall of the bowel (Elman and Cole[15]). In this investigation it has been found that the onset of shock after obstruction of the portal vein may be appreciably hastened by the intravenous injection of an isotonic saline solution. Postmortem examination of these animals revealed an intense edema of the walls of the large and small intestines. The spleen was enlarged to as much as three times its normal size.

FLUIDS AND METABOLISM

The metabolic effects of water have been investigated both in human beings and in experimental animals, and it has been shown that the administration of water increases the rate of metabolism (Eichhorst,[16] Feder,[17] Falck and Falck,[18] Genth,[19] Gruzdiev,[20] Matzkevich,[21] Becker,[22] Neumann,[23] Panum,[24] Schöndorff[25] and Weigelin.[26] However, the most direct evidence that an increased intake of fluid augments cellular activity was provided by Hawk and his co-workers,[27] when they demonstrated an increased excretion of total purine and nitrogen after the administration of fluid. The stimulating effect of water on metabolism which was demonstrated by these earlier workers was fully corroborated by subsequent investigators (Jarisch and Liljestrand,[28] Carpenter and Fox,[29] Rubner,[30] Barcroft,[31] Zuntz,[32] Verzár,[33] Tangl,[34] Janssen and Rein,[35] Lublin[36] and Grollman[37]). The degree of stimulation produced by water is largely dependent on the mode of administration. When fluid is given subcutaneously, the rise in metabolism may be absent completely. A somewhat greater response results from the oral administration of water, and it has been pointed out that the ingestion of 500 cc. of water may increase the metabolic rate in man as much as 16 per cent above the initial level (Benedict and Carpenter[38]). The intravenous ingestion of fluid causes a considerable rise in the rate of oxygen consumption. In the initial control experiments the following solutions were used: 0.9 per cent solution of sodium chloride, 5 per cent solution of dextrose and 10 per cent solution of sucrose. In each case a rise in metabolism occurred, the highest rates being encountered when dextrose solution was administered. In some instances the metabolic rate was increased by 200 to 300 per cent when dextrose solution was given, but the rise was not sustained and soon returned to the original level. Saline and sucrose solutions did not produce such great augmentations of the metabolism, which varied from 25 to 50 per cent, but the increase was longer sustained.

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[15] Elman, R., and Cole, W. H.: Hemorrhage and Shock as Causes of Death Following Acute Portal Obstruction, Arch. Surg. **28**:1166 (June) 1934.

[16] Eichhorst, H.: Ueber die Resorption der Albuminate im Dickdarm, Arch. f. Physiol. **4**:570, 1871.

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[18] Falck, E. P., and Falck, F. A.: Physiologische Studien über die Ausleerungen des auf absolute Carenz gesetzten Hundes, Beitr. z. Physiol., Hyg. u. Toxicol. **1**:1, 1875.

[19] Genth, E. A.: Untersuchungen über den Einfluss des Wassertrinkens auf den Stoffwechsel, Wiesbaden, Kreidel & Niedner, 1856.

[20] Gruzdiev, V. S.: Comparative Influence of Copious or Moderate Drinking of Water on Change of Matter, Vrach **11**:213, 1890.

[21] Matzkevich, V. G.: Influence of Abundant Water Drinking on Assimilation of Nitrogenous Particles of Food, and Nitrogenous Metabolism in Typhoid Patients, St. Petersburg, P. Voshtshinskaya, 1890.

[22] Becker, N. M.: De l'influence des solutions de bicarbonate de soude, de sel marin, d'acide carbonique et de quelques eaux alcalines sur la sécrétion du suc pancréatique, Arch. d. sc. biol. **2**:433, 1893.

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38. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations with Special Reference to the Stimulating Effect of Nutrients, Publication 261, Carnegie Institution of Washington, 1918, p. 355.

METABOLIC RESPONSE TO INJURY

Before further consideration is given to the effects of the administration of fluid in cases of shock, a brief review of the alterations in metabolism in cases of secondary shock might be presented. Secondary or traumatic shock is accompanied by a fall in the rate of oxygen consumption (Aub[39] and Henderson and co-workers[40]). In this investigation diminutions of from 30 to 50 per cent of the original rate were commonly noticed. It was found that the extent of the fall of the metabolism seemed to be dependent on the mode of production of shock (Davis[14]). Shock resulting from a single large hemorrhage is characterized by a tendency to rapid and spontaneous recovery. When severe trauma is involved, the metabolic rate has a tendency to remain fixed at a low level, and the return to normal is considerably delayed. Immediately after ligation of the portal vein, the rate of oxygen consumption

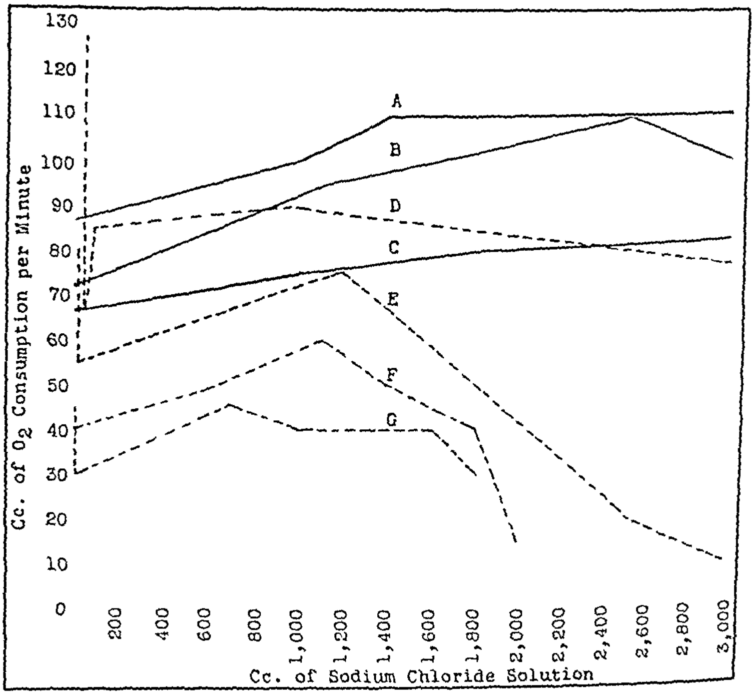

Fig. 1.—Curves showing the influence of the administration of water on the rate of oxygen consumption in normal animals and in animals in shock. *A, B* and *C* are the curves for the normal control animals; *D,* the curve for an animal in which shock was produced by extensive hemorrhage; *E,* the curve for an animal in which shock was produced by trauma plus hemorrhage, and *F,* the curve for an animal in which shock was produced by obstruction of the portal vein.

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[39] Aub, J. C.: Studies in Experimental Traumatic Shock: I. Basal Metabolism, Am. J. Physiol. **54**:388, 1920.

[40] Henderson, Y.; Prince, A. L., and Haggard, H. W.: Observations on Surgical Shock, J. A. M. A. **69**:965 (Sept. 22) 1917.

is unaffected, sometimes for an hour or more. Thereafter, a progressive downward tendency may be noted, with death as the end-result. The influence of histamine dihydrochloride is variable. Usually a fall in metabolism occurs, which in the experiments reported here has not been great. The decrease in metabolism, however, tends to be maintained for a long period. While these are the primary metabolic phenomena associated with shock, certain later changes must be taken into consideration. Within twenty-four hours an increased nitrogenous output in the urine occurs, and this is associated with a rise in metabolism (Cuthbertson[41]), which continues for periods varying from seven to ten days. This excretion of sulfur creatinine and potassium has been explained by the autolysis of injured tissues at the site of trauma.

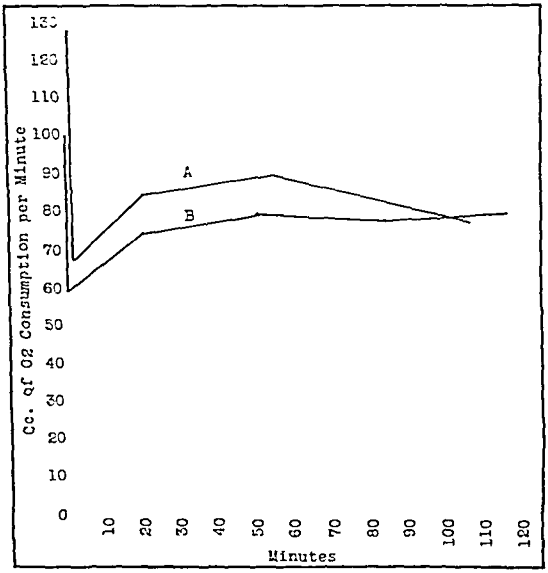

Fig. 2.—Curves showing the metabolism readings of animals which recovered spontaneously from hemorrhage. *A* is the curve of an animal that received saline solution, and *B*, the curve of an animal that did not receive saline solution.

ANOXEMIC EFFECTS OF FLUID IN SHOCK

It has been stated already that the metabolic rate of normal animals is increased by the intravenous injection of fluid. The maximal increase varies between 25 and 50 per cent and is reached only after from 1,400 to 2,400 cc. of fluid has been given. Thereafter, a plateau is obtained in the curve, and this is maintained so long as the fluid is injected and for some time afterward. Generally, the absolute increase in the rate of oxygen consumption varies directly with the initial rate of metabolism. In a normal healthy animal the tolerance for water is great. Fluid to the extent of 25 per cent of the total body weight of the animal may be given without any deleterious result.

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[41] Cuthbertson, D. P.: Observations on Disturbance of Metabolism Produced by Injury to Limbs, Quart. J. Med. **1**:233, 1932.

In traumatic shock a peculiar alteration of the metabolic response to fluids takes place. The maximal increase in the rate of oxygen usage is reached at an earlier stage during the injection of fluid, i. e., after from 700 to 1,200 cc. of the solution has been given. Thereafter, if more fluid is given, a progressive decline in the rate of oxygen consumption takes place. Apparently in shock tolerance for fluids is much diminished, as the administration of a quantity of water equivalent to only from 5 to 12 per cent of the body weight produces a fall in the metabolic rate. In this investigation it was noted that the degree of intolerance for fluids varied with the depth of shock induced. It was particularly noticeable in those animals exposed to severe trauma. Hemorrhage in small amounts did not alter the metabolic response, as such animals reacted in almost a normal manner. Shock produced by ligation of the portal vein invariably diminished the tolerance of the animal for fluid.

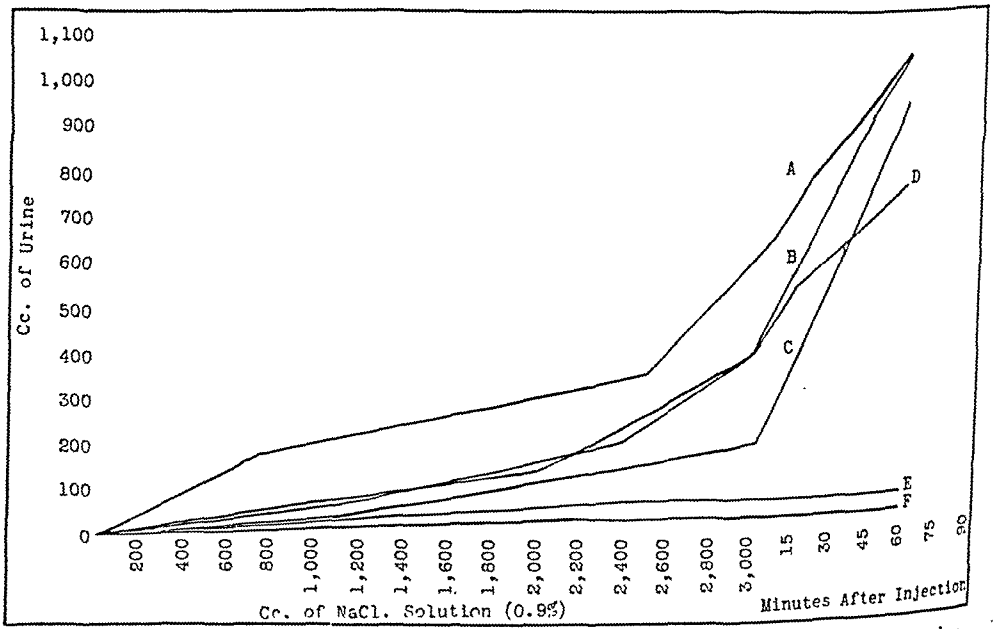

Fig. 3.—Curves showing the urinary secretion of animals in shock in relation to the administration of fluids. *A*, *B* and *C* are the curves of normal control animals. *D* is the curve of an animal in which shock was produced by the injection of histamine dihydrochloride; *E*, the curve of an animal in which shock was produced by hemorrhage, and *F*, the curve of an animal in which shock was produced by trauma.

The reason for the diminished tolerance for water of the animal in shock is difficult to state. Certainly, previous investigations point to the fact that the stimulant action of fluids on the metabolism is greatest while the fluid is in the blood vessels, and therefore can be attributed to an increase in the blood volume, rate of blood flow or both (Davis[42]). In shock, the fluid leaves the vascular bed rapidly, in spite of the existing concentration of the blood. This explains the ephemeral nature of the stimulant action of water on the rate of oxygen consumption, but it does not explain the depressant action of water in traumatic shock.

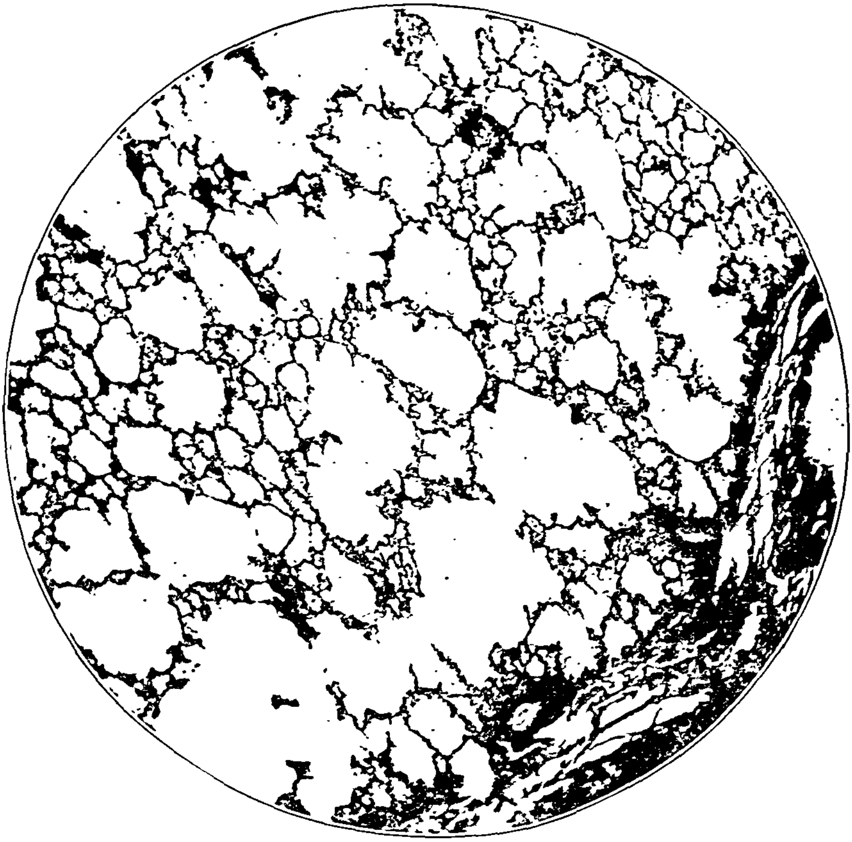

Fig. 4.—Photomicrograph of a section of the lung of an animal in which shock was produced by trauma; × 50. Acute congestion of the alveolar capillaries and minimal alveolar edema are evident.

Anoxemia, which is already present in shock, is intensified with amounts of fluid which would not affect a normal animal. In some way the transport, transfer or utilization of oxygen is affected.

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[42] Davis, H. A.: Studies in Water Balance: I. Excessive Oxygen Usage Response of Dehydrated Animals to Water and Electrolytes, Proc. Soc. Exper. Biol. & Med. **33**:242, 1935.

RENAL FUNCTION IN SHOCK

In secondary shock not only is there an alteration in the metabolic response, but there is also a change in the renal function. The injection of a 0.9 per cent solution of sodium chloride into a normal animal was followed by a brisk diuresis, which commenced shortly after the initiation of the injection. Within one hour after completion of the infusion, the urinary secretion was abundant, and volumes equivalent to one third or one half of the total amount of fluid given were obtained. In secondary shock, water diuresis is minimal, even after the infusion of large amounts of fluid. The extent of the water diuresis varies inversely with the depth of shock present.

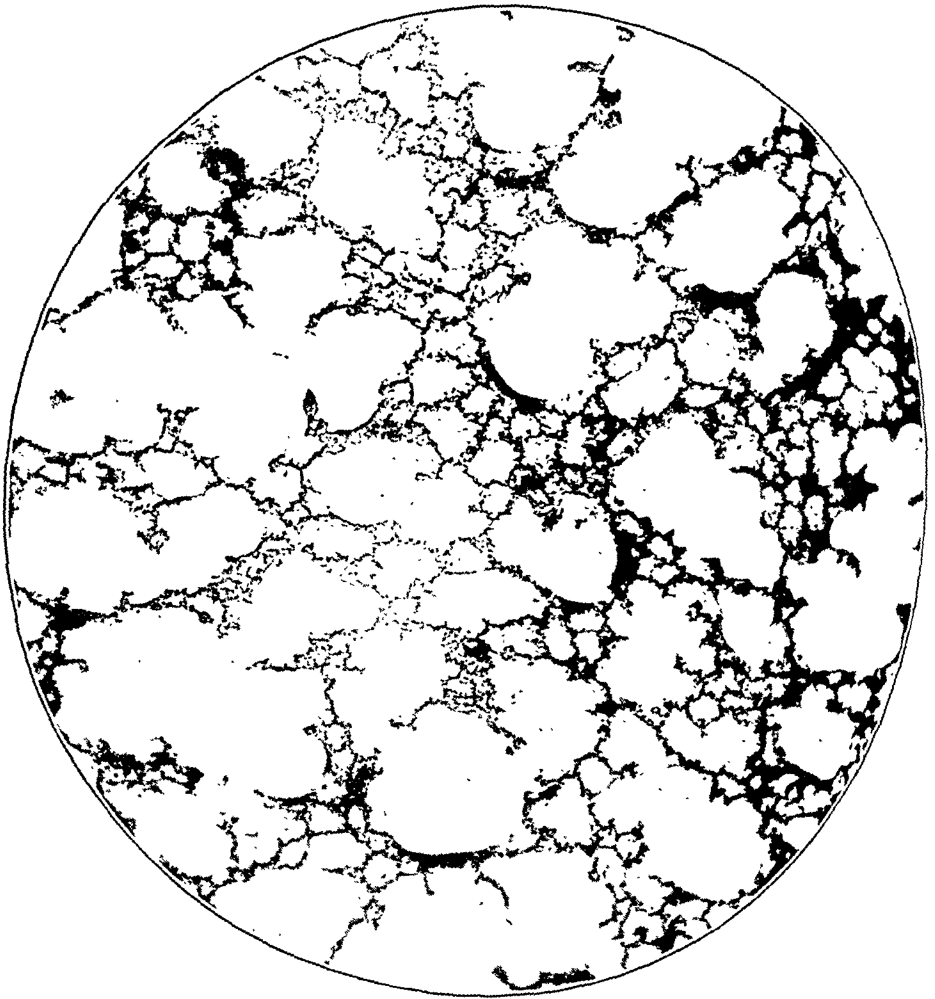

Fig. 5.—Photomicrograph of a section of a lung of an animal with traumatic shock which was treated by the administration of *fluids;* × 50. *Acute* congestion of the alveolar capillaries and moderate alveolar edema are evident.

While acidosis favors the release of water from tissues (Davis and Dragstedt[43]), its presence in association with traumatic shock is of little value. This traumatic anuria is probably related to the lowering of the filtration pressure within the glomerular capillaries. Histologic studies of kidneys removed from animals in which shock had been produced reveal the presence of an acute cloudy swelling of the tubular epithelium with pyknosis of nuclei. The glomerular capillaries are greatly congested, but no specific lesions are demonstrable. These alterations in the tissues are reversible, and no permanent renal injury

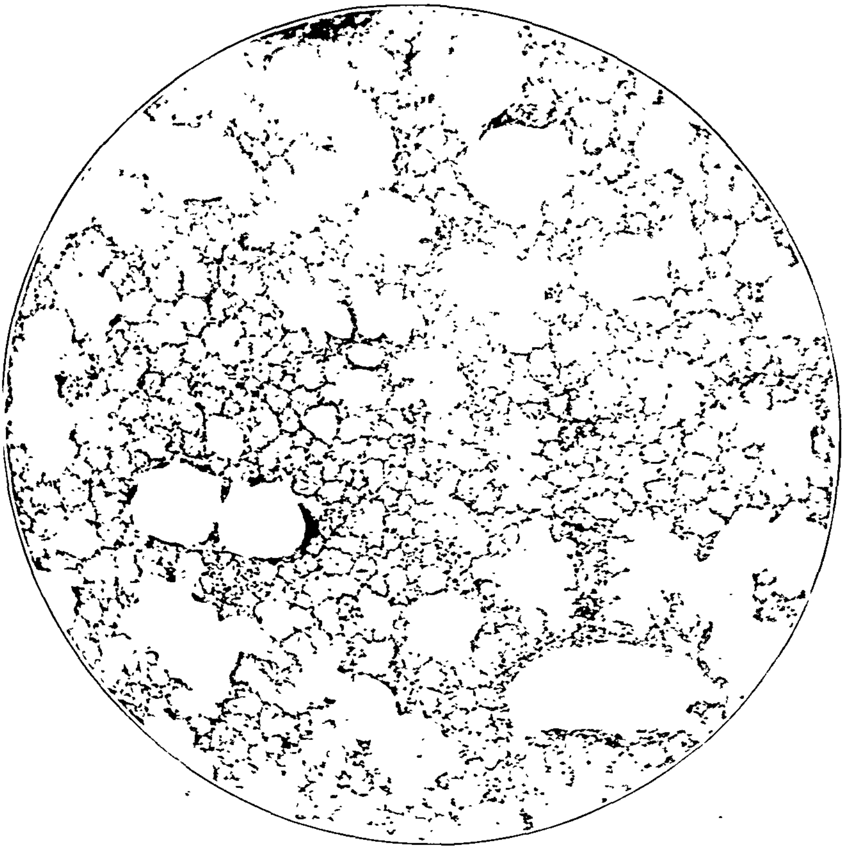

Fig. 6.—Photomicrograph of a section of the lung of a normal animal treated with fluids; × 50. No congestion of the alveolar capillaries is evident, but extensive alveolar edema may be seen.

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[43] Davis, H. A., and Dragstedt, L. R.: The Relative Significance of Electrolyte Concentration and Tissue Reaction in Water Metabolism. Am. J. Physiol. **113**:193, 1935.

occurs. However, the presence of anuria is significant, as it emphasizes the inability of the organism in shock to distribute freely within itself ingested fluids.

NATURE OF THE ANOXEMIC RESPONSE

The exact mechanism of production of the anoxemia resulting from the administration of fluids in cases of secondary shock is debatable. A diminution of oxygen usage might result from (1) an insufficiency of oxygen available to the blood in its passage through the lungs, (2) a decrease of available oxygen-carrying material and (3) interference with oxygen utilization by the cells. The third cause may, with justification, be excluded in view of the fact that the administration of large quantities of fluids sufficient to produce obvious generalized edema of

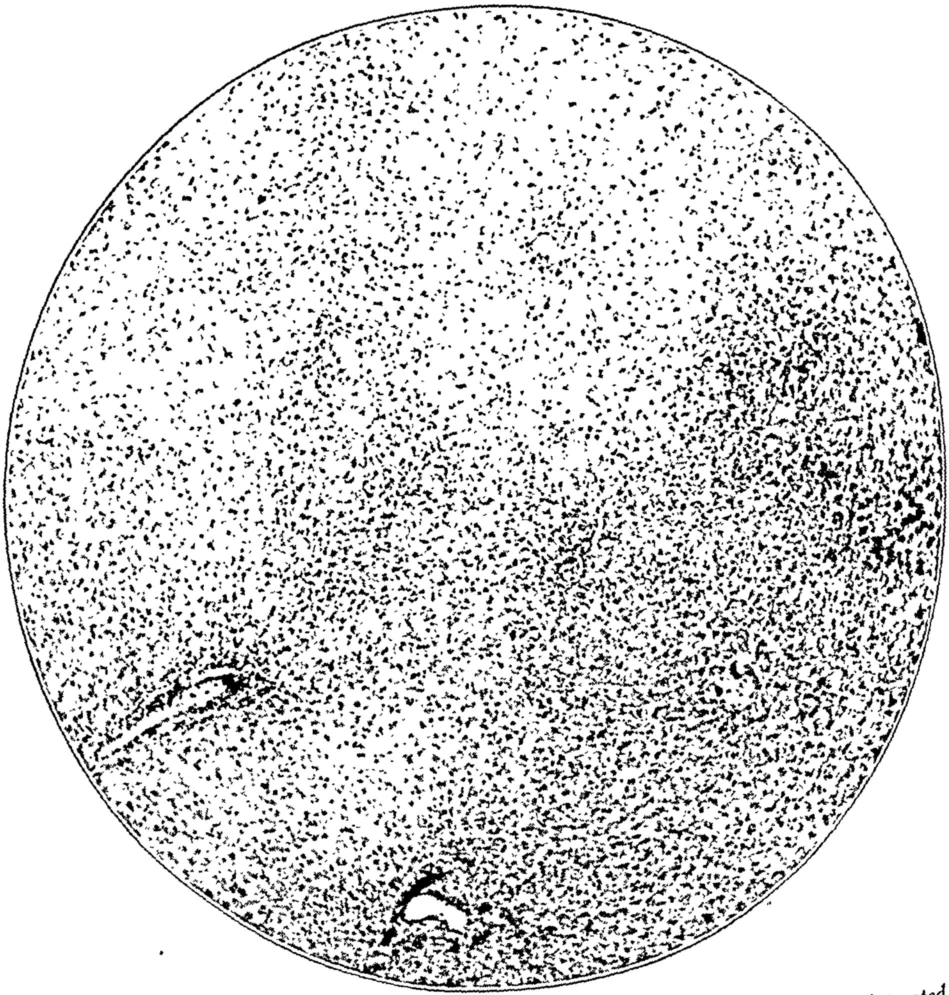

Fig. 7.—Photomicrograph of a section of the liver of a normal animal treated with fluids; × 50. Intense edema of the liver cells, with compression of the liver capillaries, and clear nuclei without pyknosis are evident.

the tissues in normal animals causes no decrease in the rate of oxygen consumption. It is possible, however, that in shock the utilization of oxygen by anoxemic tissues may be diminished by the presence of large amounts of inert fluid.

Attention was focused on the first two of these possible causes. Two subsidiary investigations were therefore undertaken. In order to examine the factor of pulmonary changes in the production of anoxemia resulting from shock with and without the administration of fluids, the following experiment was designed:

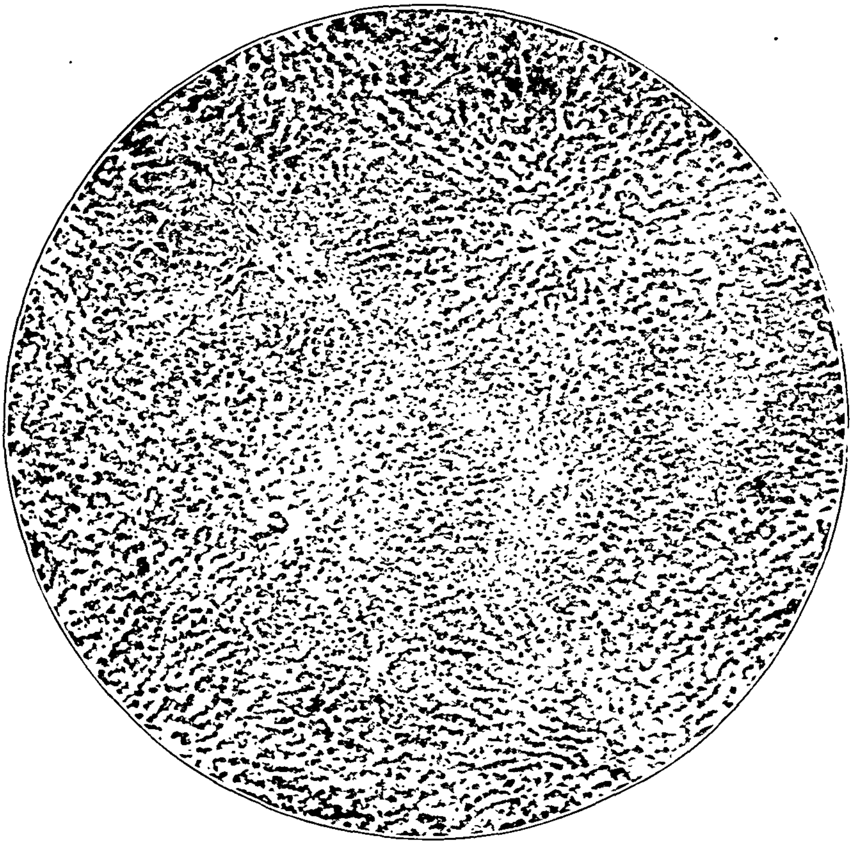

Fig. 8.—Photomicrograph of a section of the liver of an animal with traumatic shock which was treated by the administration of fluids; × 50. Acute congestion of the central capillaries with compression of the liver cells and slight nuclear pyknosis at the periphery of the nodules are evident.

A series of healthy dogs weighing from 8 to 20 Kg. was used. Pentobarbital sodium was used in a dosage of 0.03 Gm. per kilogram of body weight. Shock was induced (1) by repeated trauma to both hindlimbs and (2) by repeated hemorrhage. Kymographic tracings of the blood pressure were made. When the blood pressure was lowered to 60 mm. of mercury or less, the animal was considered to be in shock. Usually the blood pressure was maintained in the neighborhood of from 40 to 50 mm. of mercury. In order to obviate any pulmonary changes due to prolonged immobilization, the period of shock was not permitted to exceed one and one-half to two and one-half hours. Each animal was moved into various positions during the experiments. Each animal was killed either by intensification of the shock present or by air embolism, and the lungs and other viscera were immediately removed and placed in a hot diluted solution of formaldehyde U. S. P. (1:10). Four groups of experimental animals were studied: group a, animals given pentobarbital; group b, normal animals that received fluid; group c, animals in shock, and group d, animals in shock that were given fluids.

Histologic changes were absent in the lungs of the animals of group a. In the animals in group b edema was present in the alveolar spaces. This was not uniform in distribution, however, and little or no cellular reaction was observed. The histopathologic picture found in the animals of group c will be described in a forthcoming paper. The findings pertinent to the discussion here will be described. In animals in shock edema was present in scattered areas throughout both lungs. But it was not great in amount and was less than that found in the lungs of normal animals receiving fluids. In the animals of group d edema was not conspicuous and was less than that present in the animals of group b.

These findings provide no basis for the assumption that the anoxemia of shock results from pulmonary edema. Moreover, edema of the lungs does not seem to be a significant factor in the production of the anoxemia following the injection of fluids into the animal in shock.

Changes in the tissues resulting from the administration of fluids depend primarily on the state of the vascular bed. When fluids enter the circulatory system in amounts sufficient to increase the volume of circulating blood, adaptation mechanisms are at once brought into play. In table 1 are described briefly certain visceral changes accompanying the administration of fluid to normal animals and to animals in shock.

This brief summary of the visceral changes in animals in shock which received fluid and in those which did not receive fluids reveals a paradoxical phenomenon. In the animals with traumatic shock, a condition in which capillary permeability is increased, the administration of fluid produced less pulmonary edema than in the normal animals. This paradox is readily explainable by the fact that in shock much of the fluid escapes from the circulatory system at the point of least resistance—the area of trauma. It was noted in these animals that the traumatized limbs became very edematous, which would be consistent with the finding of only mild pulmonary edema, relatively little peritoneal transudate and the histologic evidence of water storage localized to the central portion of the hepatic lobules.

The final part of this investigation was undertaken to determine to what extent the use of fluid could produce a loss of protein and cellular elements from the blood of normal animals and of animals in shock. Standard amounts of fluid (60 cc. per pound of body weight) were given to the animals by vein, and the peritoneal transudate was carefully measured and examined for total proteins, albumin and globulin and for erythrocytes after centrifugation.

TABLE 1.—*Tissue Changes Resulting From Administration of Fluid in Normal and Traumatized Animals*

Viscera	Normal Animal; Fluid Administered	Animal in Shock	Animal in Shock; Fluid Administered
Lung	Considerable general edema fluid in alveoli; no capillary congestion; no cellular reaction in alveoli; no petechial hemorrhage	Mild discrete patchy distribution of edema in alveoli; marked cellular reaction with mononuclear and polymorphonuclear cells; acute congestion of alveolar capillaries with diapedesis of red blood cells; areas of hemorrhage and petechiae	Mild edema of alveoli with considerable cellular reaction—monocytes and polymorphonuclears; acute congestion of alevolar capillaries with diapedesis of red blood cells; areas of hemorrhage in alveoli; subpleural petechiae
Kidney	Slight increase in size; distention of Bowman's capsule; no glomerular lesions; tubular epithelium normal with large vesicular nuclei and well defined chromatin material	Slight diminution in size; acute cloudy swelling of tubular epithelium with small pyknotic nuclei; congestion of glomerular capillaries	Early cloudy degeneration of tubular epithelium with small pyknotic nuclei; no glomerular lesions
Liver	Larger than normal; marked edema and vacuolization of liver cells; nuclei large, clear and vesicular, with well defined chromatin material; moderate capillary dilatation in region of central vein	Slightly larger; marked congestion of liver capillaries in region of central vein; liver cells small, compressed with small pyknotic nuclei	Slightly larger; mild edema and vacuolization of hepatic cells around central vein where nuclei are large and vesicular; cells stain deeply with small pyknotic nuclei in periphery of lobule
Spleen	Enlarged; edema of splenic pulp spaces; dilatation of splenic sinusoids	Small; congestion of splenic sinusoids	Small; congestion of splenic sinusoids
Heart	Moderate dilatation—right auricle and ventricle; no histopathologic changes	Contracted; no histopathologic changes	Moderate dilatation; no histopathologic changes
Pancreas	No specific pathologic process	No specific pathologic process	No specific pathologic process

The representative data, shown in table 2, suggest that in the intact animal the administration of fluid leads to a loss of albumin and globulin from the blood stream. The loss of protein into the peritoneal fluid is 9.5 per cent (calculated on the basis of a blood serum content of 7 Gm. per hundred cubic centimeters of blood). The percentage of protein lost in the animal in shock that is treated with fluid is equal to, and probably greater than, that found in the intact animal. It will be noted that in dogs 3 and 4 the percentage calculations have been made on the basis of normal calculated volumes of blood. As the volume of blood is reduced in traumatic shock, the percentage of protein lost in animal 3 is probably higher than is shown by table 2.

COMMENT

This study seems to indicate the presence of certain physiologic and pathologic limitations to the free and equal distribution of fluids in the organism in shock. The introduction of fluid into the intact animal produces a dilution of the blood with subsequent diuresis. With larger amounts of fluid, the liver cells imbibe water from the blood stream and become edematous, ultimately causing compression of the hepatic capillaries. Still later, the splenic sinusoids dilate. A transudate of protein-laden fluid occurs into the peritoneal cavity. Finally, the fluid containing serum albumin and globulin permeates through the capillary walls, particularly those of the lungs, leading to pulmonary edema. In secondary shock the normal reservoir action of the blood for fluids is lost, and fluid leaves the blood stream more rapidly than in the intact animal (Davis [44]). The site of fluid loss is greatest in the region of trauma, so that relatively little transudation of fluid occurs into the peritoneum or into the alveoli of the lungs. Evidences of water imbibition are present in the central portions of the hepatic lobules. It cannot be stated definitely here whether or not this localization of water storage by the liver is indicative of inability of the liver cells to store water or of an insufficient quantity of water available for storage. The production of a lowered rate of oxygen consumption by the administration of fluids in cases of secondary shock does not result from interference with the supply of available oxygen by pulmonary edema. The stimulant action of water on metabolism is exerted only so long as fluid is actually present

TABLE 2.—*Effect of Sodium Chloride Solution (0.9 Per Cent) on Protein Loss into Peritoneal Cavity*

					Peritoneal Fluid			
Dog No.	Type of Experiment	Calculated Blood Volume, Cc.	Calculated Total Protein in Blood, Gm.	Peritoneal Fluid, Cc.	Total Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin Gm. per 100 Cc.	Protein Loss, %
2	Control animal; fluid administered	738	51.0	250	4.87	3.78	1.09	9.5
3	Animal in shock; fluid administered	553	38.5	100	3.59	2.79	0.80	9.3
4	Animal in shock (traumatic)	1,353	94.5	10	5.70	4.20	1.50	0.6

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44. Davis, H. A.: The Behaviour of Isotonic and Hypertonic Solutions in the Blood Stream of Normal and Dehydrated Animals, Proc. Soc. Exper. Biol. & Med. **32**:210, 1934.

within the circulatory system and seems to depend on the resultant increase of blood volume or blood flow (Davis[42]). Removal of serum albumin and globulin and of blood cells by the introduced fluid into the area of trauma and peritoneal cavity diminishes the material available for transportation of oxygen and leads to a still greater degree of oxygen want.

CONCLUSION

In traumatic shock a peculiar alteration of the response to fluids exists. The physiologic availability of water is diminished even to the point of actual intolerance (Davis[45]). Even the transfusion of blood, as has been pointed out by Zunz and Govaerts,[46] can be harmful. The administration of a quantity of fluid equivalent to from 5 to 12 per cent of the body weight may result in a fall in the metabolic rate. The intact animal, on the contrary, may be given fluid to the extent of 25 per cent of the total body weight without any diminution in the rate of oxygen consumption. The anoxemia of traumatic shock is augmented by the administration of fluids, which promote a loss of protein and cells into the traumatized area, into the peritoneal cavity and, to a slight extent, into the alveoli of the lungs and general tissue spaces.

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45. Davis, H. A.: Influence of Water Administration upon Oxygen Consumption Rate in Shock, Proc. Soc. Exper. Biol. & Med. **34**:21, 1936.

46. Zunz, E., and Govaerts, P.: Recherches expérimentales sur les effets de la transfusion dans les divers états de collapsus circulatoire, Bull. Acad. roy. de méd. de Belgique **29**:796, 1919.

EXTENSIVE BURNS

TREATMENT WITH SILVER NITRATE AND METHYL ROSANILINE

HIRA E. BRANCH, M.D.
DETROIT

The ideal treatment for burns is one that, first, saves the patient's life; second, eliminates pain, shock and toxemia; third, reduces the morbidity to a minimum, and fourth, allows the burned area to heal quickly without skin grafting being necessary.

The method of treating burns to be brought out in this paper approaches closely to the "ideal" treatment, as may be seen by the accompanying table. First, there have been no deaths in cases in which the treatment has been used thus far, and there were only seven deaths in ninety-five cases in which this form of therapy was used during its development. Second, the period of pain and shock was very short. Toxemia did not develop as a serious threat. Third, the morbidity was greatly reduced, for the patients were turned about in a few hours and were urged to get up and about in a few days and to wait on and amuse themselves. Fourth, skin grafting was done in only one case. However, the mere use of this combination treatment for the local area did not do all the aforementioned things alone; naturally measures for the general upbuilding of the patient were also carried out.

BRIEF RÉSUMÉ OF MODERN TREATMENTS FOR BURNS

In 1925 the late Dr. Edward C. Davidson[1] published his famous paper entitled "Tannic Acid in the Treatment of Burns," in which the use of compresses on the injured areas was advised, a 2.5 per cent aqueous solution of tannic acid being employed. Attempts to make a satisfactory ointment of tannic acid at that time failed, chiefly because an oily base was used. Later, a spray of a 5 per cent aqueous solution of tannic acid was used in place of the compresses. There is now little question but that the spray did revolutionize the manner of dealing with burns. The mortality rate has been lowered from 35 or 38 per cent to 10.5 or 12 per cent. Later, this treatment was altered somewhat by the use of a 5 per cent tannic acid gel, a mixture of tannic acid in a water-

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The experimental work for this monograph was done at the Children's Hospital of Michigan, while the author was in the surgical service.

[1] Davidson, E. C.: Tannic Acid in the Treatment of Burns, Surg., Gynec. & Obst. **41**:202-221 (Aug.) 1925.

soluble base. The principles of treatment are the same with the gel as with the solution, but the tanning process is much slower with the former.

There were little or no changes of note in the management of burns from 1925 till 1932, as far as the treatment of the local area was concerned. Big strides were made in treating the general condition of the patient, the water balance and the chloride and plasma protein contents being carefully watched. However, this has been dealt with elsewhere. In 1932 Dr. Robert Henry Aldrich[2] read a paper in Boston on "The Role of Infection in Burns," which dealt with the theory and treatment of burns with special reference to methyl rosaniline (gentian violet). The mortality rate for burns treated with this drug dropped to the same level as that for burns treated with tannic acid, namely, from 10 to 12 per cent. The methyl rosaniline was sprayed on the burned area in the form of a 1 per cent aqueous solution. Again a gel was made, the methyl rosaniline being used in a water-soluble base. This gel has been used chiefly in the treatment of ambulatory patients with minor burns and is an excellent way of dealing with them. A generous coat of the gel is spread over the burn, and a bandage is applied which is not removed for about ten days. Practically all burns are cleanly healed in that time.

The next step forward was taken by Dr. A. G. Bettman[3] in 1935, when he combined the use of a solution of silver nitrate over one spray of tannic acid, thus obtaining an immediate black crust over the injured surface. This saved about four hours in the tanning process. However, the disadvantages and the advantages of this method were the same after the first few hours as those of the tannic acid alone. Perhaps it is now advisable to list the advantages and disadvantages of the aforementioned treatments.

ADVANTAGES AND DISADVANTAGES OF VARIOUS METHODS OF TREATMENT

Tannic Acid.—Herewith are quoted some of Dr. Davidson's conclusions as to the advantages of treatment with tannic acid:

> Coagulation of the devitalized tissue by the use of tannic acid lessens toxemia.
>
> Tannic acid as an initial dressing has an analgesic effect.
>
> The subsequent use of the open air method causes minimal trauma and promotes general comfort.

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[2] Aldrich, R. H.: The Rôle of Infection in Burns, New England J. Med. **208**:299-309 (Feb. 9) 1933.

[3] Bettman, A. G.: Tannic Acid-Silver Nitrate Treatment of Burns, Northwest Med. **34**:46-51 (Feb.) 1935.

[4] Davidson, E. C.: The Prevention of the Toxemia of Burns: Treatment by Tannic Acid Solution, Am. J. Surg. **40**:114-115 (May) 1926. Davidson.[1]

The local astringent effect prevents the loss of body fluid.

Secondary infection is limited by this method of treatment because of the absence of a favorable nidus for bacterial growth.

Scar tissue formation has been lessened.

The protective layer of coagulated protein forms a scaffold for the growth of the young epithelial cells over the denuded surface.

The tannic acid treatment has brought a decided drop in the mortality rate for burns.

A uniform method of dealing with burns has been established throughout the world.

Some of the disadvantages of the treatment with tannic acid are:

1. The patient must remain quiet while covered with the black coagulum, otherwise cracking occurs. This stationary position favors pneumonia and aural infections and does not promote the "will to live" spirit so often needed by the patient with an extensive burn.

2. Cracking of the coagulum brings about infection, which usually requires removal of the crust.

3. The coagulum sticks tenaciously to the third degree areas of the burn, requiring surgical removal. (The soaking of a tannic acid crust is contraindicated because of infection and toxemia.)

4. Surgical removal of the black coagulum destroys many islands of epithelium beneath, which invariably necessitates skin grafting to the denuded areas.

Methyl Rosaniline Spray.—The advantages of using a spray of methyl rosaniline solution are the same as for tannic acid, with the following differences:

1. The crust that forms is pliable, but if it should crack the area is merely resprayed and infection is limited.

2. Infection is prevented, and if it is present before treatment is started methyl rosaniline helps to eradicate it.

3. Débridement of the burn does not have to be as severe.

4. The crust formed by methyl rosaniline can be soaked off, thus preserving the epithelial islands beneath. This practically eliminates skin grafting.

The disadvantages of this type of treatment are:

1. The solution has no astringent effect and does not prevent loss of body fluids.

2. The crust takes from one to three days to form, owing to the fact that the devitalized proteins are not coagulated.

Silver Nitrate-Tannic Acid Treatment.—Except for the rapid tanning effect and the saving of a few hours in that respect, the advantages and the disadvantages of this combination of drugs are practically the same as those for tannic acid alone.

EVOLUTION OF THE SILVER NITRATE-METHYL ROSANILINE TREATMENT

The principles of the treatment of burns with tannic acid are sound. This has been proved by the late Dr. Davidson and others. Clear evidence has been shown by the decrease in mortality from about 35 per cent to about 10 or 12 per cent. However, the solution is contraindicated in infected areas or surfaces that bend or are subject to infection, such as the perineum, fingers, toes, scalp, etc. During 1935 I experimented with various combinations of treatments, always using tannic acid as the basic treatment, chiefly because of its beneficial qualities and also because Dr. Grover C. Penberthy, with the late Dr. Davidson, had thoroughly established that form of treatment at the Children's Hospital of Michigan, in Detroit, where this work was done.

The first combination tried was the use of a spray of a 5 per cent solution of tannic acid on all clean areas that did not require motion or were not subject to infection. A 1 per cent aqueous solution of methyl rosaniline was used on all areas that were either infected or likely to become infected. The results were a great improvement over those obtained with tannic acid alone. The next modification was the combination of silver nitrate with the tannic acid on the clean areas and methyl rosaniline on the potentially dirty surfaces. The results were about the same as with the first combination.

The disadvantages have all been listed previously. However, the main ones were that the patient had to remain quiet for from two to three weeks, sometimes with his extremities in slings off the bed. The crust formed by the tannic acid had to be removed surgically from the deeper burned areas, necessitating skin grafting. The methyl rosaniline did not form an immediate crust and stop the loss of body fluids. The next problems were to find a combination which not only would stop these abuses but would keep the mortality rate down, prevent pain, shock and toxemia, reduce the morbidity (absolute rest in bed chiefly), and lastly, allow the burned surfaces to heal quickly without skin grafting. The methyl rosaniline prevented infection and toxemia and reduced morbidity and the amount of skin grafting, but the pain, shock and loss of body fluids were not eliminated. and the mortality rate was still about 10 to 12 per cent. The crusts formed by the tannic acid prevented pain and toxemia if infection did not occur. However, the morbidity and skin grafting were not lessene remained about the same. Methyl rosaniline acid to give any advantageous qualities. Silve merely formed a black crust immediately over t black crust was due partly to a precipitation of tannate and partly to a coagulation of the dev

The next combination used was silver nitrat The results were excellent. The 10 per cent acted on the proteins of the serum exuding f immediately lay down a milky white coagulum the place of tannic acid in coagulating the prot loss of body fluids. The methyl rosaniline stai and aided in destroying and preventing infection. of three weeks that the second degree burns crust had cracked off. The third degree areas violet coagulum, but this was easily removed b and by the use of compresses. On soaking o invariably enough epithelial islands beneath so th necessary. After the coat was off compresses so chloride, 1:200 solution, or compresses or gauze was used to stimulate epithelization of the den period of pain and shock was practically elim toxemia rarely developed. The amount of pa fluids necessary was greatly reduced. The m decreased, for the patients could be freely turned after the first few days they could be removed f allowed to walk about. Their general spirits im

During 1935, the transition period from trea to the new silver nitrate-methyl rosaniline method patients treated whose burns were severe enou pitalization. Of these, seven died, giving a mor cent. In 1936, through June, eighteen patients wit to necessitate hospitalization were treated by th rosaniline method. The results are presented in panying table. There were no deaths; all the about during their recovery, unless they were too period of hospitalization was very short. Only skin-grafting operation. The highest temperature

Data on Burns Treated by Silver Nitrate and Methyl Rosaniline

Case	Sex	Color	Age*	Age of Burn, Hr.	Etiology	Previous Treatment	Degree of Burn	Extent of Body Surface, %	Location	Period of Complete Rest in Bed	Period of Hospitalization, Days	Highest Temperature (R.)	Average Temperature (R.)	Skin Grafting	Results
1	M	W	2½	24	Fire	Olive oil	2-3	20	Head; neck; back	5 days	27	102.0	100.0	0	Recovery
2	M	W	1	4	Coffee	Oil	2-3	20	Chest; right thigh; abdomen; perineum	2 days	18	102.0	99.4	0	Recovery
3	M	W	1½	18	Water	Ointment	2	15	Buttocks; back; thighs	8 days	13	101.6	99.0	0	Recovery
4	M	W	8	24	Water	Ointment; oil	3	35	Head; neck; back; arms	6 days	62	102.0	100.0	1	Recovery
5	F	W	3½	48	Fire	None	2	12	Face; chest; left arm	1 day	10	101.6	99.8	0	Recovery
6	M	W	11	9	Coffee	Lard; ointment	2-3	15	Abdomen; perineum; thighs	5 days	18	102.4	100.0	0	Recovery
7	M	W	10 mo.	1	Water	None	3	18	Head; trunk; left arm	8 days	32	105.1	100.8	0	Recovery
8	F	W	9	1	Water	Ointment	2-3	10	Left side of body; arm; leg	1 day	6	101.4	99.8	0	Improvement
9	M	W	1	20	Coffee	Ointment	3	12	Chest; right arm	7 days	12	102.4	99.8	0	Recovery
10	M	W	2½	1	Water	None	2-3	30	Trunk; right arm; left leg	2 days	14	100.4	99.0	0	Improvement
11	M	W	7 mo.	11	Cleaning solution	Tannic acid gel	2-3	25	Trunk; thighs	1 day	22	101.8	100.6	0	Recovery
12	M	N	2	1	Water	None	2-3	25	Neck; trunk; arms	5 days	22	101.4	101.0	0	Recovery
13	F	W	8	2	Fire	None	2	8	Face; neck; chest	4 hours	13	101.2	99.0	0	Recovery
14	M	W	1	1	Water	Oil; ointment	3	35	Head; trunk; right arm	6 days	35	101.0	100.4	0	Recovery
15	M	N	7	1	Water	Oil	2	8	Head; neck; chest	2 days	16	102.6	99.4	0	Recovery
16	F	W	2	1	Water	Oil; tannic acid ointment	2-3	12	Back; perineum	1 day	18	100.2	99.0	0	Recovery
17	F	W	1	3	Water	Ointment	2	10	Arms; legs; chest	2 days	6	102.2	100.0	0	Improvement
18	M	W	1	2	Water	None	2	5	Left leg; perineum	3 days	3	100.6	99.6	0	Improvement

* Unless otherwise stated, the age is given in years.

ROUTINE TREATMENT WITH SILVER NITRATE-METHYL ROSANILINE

After the patient is burned, the following procedures are carried out:

1. A large dose of sedative is given—codeine or morphine sulfate with phenobarbital.

2. The burned areas are washed with tincture of soft soap.

3. Débridement of the burn is done lightly and rapidly by merely breaking the blisters and removing the loose skin. The area is then washed with a sterile saline solution or a solution of boric acid.

4. The burn is sprayed at once with a 1 per cent aqueous solution of methyl rosaniline, and after three or four minutes the entire burned area is swabbed with a 10 per cent solution of silver nitrate.

5. The patient is placed in a burn tent at a temperature of 85 to 90 C. The area is resprayed with a 1 per cent solution of methyl rosaniline every fifteen minutes for about five times. After that the spray is used once or twice a day only if necessary.

6. Fluids are forced strongly by mouth.

7. Hypodermoclysis of physiologic solution of sodium chloride is given every six or eight hours, as indicated by the patient's condition.

8. Fluids are given intravenously only if the temperature rises to 103 F.

9. Transfusion is done if necessary.

10. The patient is moved about as soon as the crust is established and is allowed to walk about as soon as the period of shock is over and if no signs of toxemia develop. The patient is gotten up and about regardless of the size or location of the burned area and usually may walk about freely after the first twenty-four hours if the burn is small, covering up to about 20 per cent of the body surface. It is perhaps safer to keep the patient with the more extensive burn in bed from five to seven days, or at least till the temperature has been normal for about twenty-four hours.

11. If any coagulum remains at the end of two and one-half or three weeks, it should be soaked off with brine or by compresses. Compresses treated with cysteine hydrochloride, 1:200 solution, may then be applied to the third degree areas that are not healed, alternating every four days with compresses soaked in boric acid or gauze treated with scarlet red may be applied to stimulate epithelization.

SUMMARY AND CONCLUSIONS

A treatment for extensive burns which employs silver nitrate and methyl rosaniline has been presented in detail.

During the experimental period ninety-five patients were treated with various combinations of solutions, and the mortality rate was only 7.3 per cent.

Since the establishment of the silver nitrate-methyl rosaniline therapy, eighteen additional patients have been treated, with no deaths. The data in these cases have been presented in detail.

A simple method of dealing with minor burns in ambulatory patients has been presented, methyl rosaniline being used in a water soluble base.

The principles set up for the treatment of burns with tannic acid have been upheld with this form of therapy, even though that solution was not used, and, in addition, there are several advantages.

Shock and pain were held at a minimum.

Toxemia rarely developed as a clinical threat.

Infection rarely became a severe complication, regardless of the location of the burned area.

Patients were moved about freely after the first few hours and were urged to get up in wheel chairs or to walk in a few days regardless of location of the coagulum or its extent.

Burns healed quickly; the period of hospitalization was very short.

Skin grafting was rarely, if ever, necessary to get the patient quickly covered with epithelium.

Scar tissue was held at a minimum.

Urinalyses done as a routine showed no renal complications.

The general outlook of the patients was extremely good as soon as the period of pain and fright was over.

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MENINGOCOCCIC MENINGITIS COMPLICATING FRACTURE OF THE SKULL

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Acute purulent meningitis complicating fracture of the skull and caused by pyogenic cocci is well known, but meningococcic meningitis occurring under similar conditions has been infrequently reported. Four such cases have recently been observed at the Bellevue Hospital and are being reported because of their therapeutic indications and forensic importance.

A study of the relationship of trauma and fracture of the skull to meningococcic meningitis was reported by Seligmann and Pieper.[1] Of 674 cases of meningococcic meningitis, a history of trauma was recorded in 55, but fracture of the skull was demonstrated in only 2. In 21 of their cases, including the 2 in which there was fracture of the skull, meningitis appeared from one to three days after trauma. In 17 cases trauma preceded the onset of meningitis by from eight days to three months, and in 17 others a period of from four months to two years elapsed between trauma and the onset of meningitis. The authors asserted that in several of these cases the causal relationship between trauma to the head and meningococcic meningitis appeared unequivocal and that in the majority of the others the existence of this relationship was at least probable.

In 8 other cases a similarly long interval (from twelve days to eight months) is recorded between the time of trauma to the head[2] or frac-

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[1] Seligmann, E., and Pieper, E.: Die Cerebrospinalmeningitis in Preussen in den Jahren 1923 und 1924, Veröffentl. a. d. Geb. d. Med.-Verwalt. **20**:441, 1926.

[2] Reiche, F.: Der senile Typus der übertragbaren Genickstarre, München. med. Wchnschr. **56**:1829 (Sept. 7) 1909. Gutzeit, K., and Stern, R.: Trauma und epidemische Meningitis, Med. Klin. **25**:1400 (Sept. 6) 1929.

ture of the base of the skull[3] and the onset of meningococcic meningitis. In other reports, however, the interval was briefer. In 7 cases[4] meningococcic meningitis followed fracture of the skull within from one to eight days, and in 5 cases of trauma to the head but no fracture of the skull[5] from one to four days elapsed before the development of meningococcic meningitis. In a case of trauma to the head with fracture of the nasal bones[6] meningococcic meningitis was observed eighteen hours after the injury.

REPORT OF CASES

CASE 1.—M. Z., a 52 year old white man, was admitted to the psychiatric service on April 16, 1934, because of an injury to the head. He appeared acutely alcoholic and showed contusions of the nose, epistaxis and projectile vomiting. The temperature was normal, and the spinal fluid, bloody. On April 18 the temperature rose to 103 F., but the spinal fluid was unchanged. On April 19 the spinal fluid was xanthochromic. On April 21 there were stiffness of the neck and a positive Kernig sign, and the spinal tap revealed purulent fluid containing micro-organisms which were identified on culture as meningococci.[7] Three additional cultures of the spinal fluid in the subsequent week confirmed the presence of meningococci, and although antimeningococcus serum was given intrathecally at daily intervals, death occurred on May 2, sixteen days after the patient's admission to the hospital.

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[3] Schmidt, P.: Pneumokokken- und Meningokokken-Meningitis nach Schädelbasisfraktur, Deutsche med. Wchnschr. **42**:124 (Feb. 3) 1916. Terbrüggen, R.: Ein weiterer Fall von epidemischer Zerebrospinalmeningitis nach Schädelbasisfraktur, Ztschr. f. Laryng., Rhin., Otol. **18**:312 (Aug.) 1929. Gruber, G. B.: Zur Lehre von Wesen, Verbreitung und Bekämpfung der Meningokokken-Meningitis, Ztschr. f. Hyg. u. Infektionskr. **80**:219 (Aug. 18) 1915. Lode, A., and Schmuttermayer, F.: Traumatische Meningokokken-Meningitis, Wien. klin. Wchnschr. **42**:5 (Jan. 4) 1929. Macgraith, B. G., and Adel, M. B.: Meningococcal Meningitis Following Fracture of the Skull, Lancet **1**:863 (April 13) 1935. Aronowitsch, G. D.: Meningitis und Trauma (Ueber Fälle von Meningokokken- und Pneumokokkenmeningitis nach Kopfverletzung), Deutsche Ztschr. f. Nervenh. **129**:73 (Dec. 22) 1932.

[4] Torrance, A. M.: Meningococcus Meningitis Following Head Injuries, Clin. Med. & Surg. **37**:898 (Dec.) 1930. Korbsch, H.: Meningitis cerebrospinalis epidemica nach Schädeltrauma, Arch. f. Psychiat. **70**:221, 1923-1924. Kalb, A.: Ueber Meningokokkenmeningitis nach Schädeltraumen, Beitr. z. klin. Chir. **124**:211, 1921. Voss, O.: Epidemische Zerebrospinalmeningitis im Anschluss an Schädelbasisfrakturen, Ztschr. f. Laryng., Rhin., Otol. **17**:221 (Dec.) 1928. Lindstrom, E.: Meningitis cerebrospinalis post traumam, Hygiea **5**:708 (July) 1905.

[5] Busi, A.: Intorno a un caso di meningite cerebro-spinale traumatica, Arch. di psichiat. **26**:497, 1905. Richey, de W. G., and Helmbold, T. R.: A Case of Meningococcic Meningitis Following Head Injury, Am. J. M. Sc. **166**:559 (Oct.) 1923. Munk, W.: Den traumatiske purulent meningitis, Bibliot. f. læger **119**: 218 (Feb.) 1927. Brändle, U.: Trauma und Meningitis, Dissert., Vienna, Holzworth and Berger, 1932. Jakob, F.: Posttraumatische Meningokokken-Meningitis, Schweiz. med. Wchnschr. **64**:630 (July 7) 1934.

[6] Weitzel, L., and Martin, L.: Rechute de méningite cérébro-spinale après un traumatisme crânien, Presse méd. **34**:1211 (Sept.) 1926.

[7] In all 4 cases the identification of the micro-organism was determined by fermentation and agglutination reactions.

Necropsy revealed a vertical fracture of the occipital bone with extension into the right petrous bone. There were contrecoup lacerations of the brain and subdural hemorrhage. A slight hemorrhage was encountered in the sphenoid sinus, but the ethmoid sinuses and middle ears showed no suppuration. There was an abundant collection of greenish purulent exudate over the vertex and the dorsal surface of the cerebellum.

Case 2.—J. T., a 61 year old white man, was admitted to the psychiatric service on May 16, 1936. The patient was irrational and could give no account of himself. Examination disclosed abrasions over the occipital region of the scalp and contusions over the left frontoparietal area and left thigh. Caked blood was found in the nares. The temperature was 98.6 F., and the spinal fluid was bloody. During the first two days the patient remained confused and disoriented. On May 19 the temperature rose to 103.2 F., and stiffness of the neck and a positive Kernig sign were elicited. The spinal fluid was xanthochromic and contained many polymorphonuclear leukocytes and gram-negative intracellular diplococci, which were identified on culture as meningococci. Antimeningococcus serum was given daily by the intraspinal route, but the patient died on May 22, six days after admission to the hospital.

At neropsy a fracture of the skull was encountered which ran about ¾ inch (1.9 cm.) to the left of the occipital apex down into the foramen magnum and extended up between the vascular process in the occipital portion and the left temporal bone through the sella turcica longitudinally. There was a laceration of the brain on the under-surface of the frontal and temporal lobes on the right side. A leptomeningitis of the purulent type was found around the pons and the cerebellum.

Case 3.—L. D., a 49 year old white man, was admitted to the psychiatric service on May 1, 1936. The patient was found on the street in a stupor, and no history could be obtained. Examination revealed dried blood in the nares and in the left external auditory canal. The temperature was 99.6 F., and the spinal fluid was bloody. During the next ten days the patient appeared rational and was afebrile, though he complained of headache. On the tenth day, because of persistence of the headache and the elevation of the temperature to 104 F., the spinal tap was repeated, and the fluid contained many polymorphonuclear leukocytes and gram-negative diplococci, which were identified on culture as meningococci. A daily spinal tap also showed the fluid to contain meningococci. The patient was daily given intraspinal injections of antimeningococcus serum and appeared to be doing well until acute parotitis developed. He died on June 2, thirty-two days after admission to the hospital.

At necropsy a transverse fissure fracture was noted in the petrous portion of the left temporal bone. The cells of the left middle ear and mastoid contained greenish yellow pus. The air cells of the right ear and mastoid and the right sphenoid and ethmoid sinuses were normal. Reddish brown discoloration of the dura was found over the right parietal and occipital regions. A greenish yellow purulent exudate was encountered in the cisterna magna.

Case 4.—S. Z., a 27 year old professional wrestler, was admitted to the psychiatric service on June 1, 1936. On May 26, while engaged in a wrestling match, he was thrown out of the ring. Shortly thereafter he went to his hotel, where he fell out of a second story window. No record is available of his course previous to the admission to the hospital, except that he had been disoriented and violent. On admission he appeared quiet and cooperative and presented multiple contusions. The spinal fluid was purulent and contained meningococci in pure culture. Antimeningococcus serum was given intrathecally, but deepening stupor appeared and death occurred forty hours after the patient's admission to the hospital. Culture of the final spinal puncture fluid yielded meningococci and type II pneumococci.

At necropsy a fissure fracture, about 1 cm. in length, was found in the petrous portion of the left temporal bone. Blood was encountered in the right middle ear, but the left middle ear, the mastoid cells and the sphenoid and ethmoid sinuses contained neither blood nor pus. A purulent leptomeningitis was present over the the vertex of the brain.

COMMENT

All 4 patients exhibited the coexistence of fracture of the skull and meningococcic meningitis. In cases 1, 2 and 3 the sequence of events appears clear, in that meningococcic meningitis followed fracture of the skull in five, three and ten days, respectively. In case 4 meningitis was present when the patient was first observed, and the sequence of events is therefore uncertain. It is possible but not probable that the patient had meningitis at the time of the wrestling match.

Although it is to be admitted that these 4 cases and the 16 cases reported in the literature are too few to establish definitely the direct causal relationship between fracture of the skull and meningococcic meningitis, certain considerations support this view. That the meninges may become readily invaded by pathogenic micro-organisms from the nasopharynx after fracture of the skull is well illustrated by the frequent cases of pneumococcic meningitis which occur following fracture of the base of the skull (Vance[8]). Therefore, when meningococci are present in the nasopharynx, it is to be expected that they too may invade and reach the subarachnoid space if the barrier between the nasopharynx and the meninges suffers injury. It is well known that meningococci are present in the nasopharynx of carriers and from time to time in otherwise normal persons.[9] It is also known that the disease

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8. Vance, B. M.: Fractures of the Skull: Complications and Causes of Death: Review of Five Hundred and Twelve Necropsies and of Sixty-One Cases Studied Clinically, Arch. Surg. **14:**1023 (May) 1927.

9. (*a*) Albrecht, H., and Ghon, A.: Ueber die Aetiologie und pathologische Anatomie der Meningitis cerebrospinalis epidemica, Wien. klin. Wchnschr. **14:** 984 (Oct.) 1901. (*b*) Zinsser, H., and Bayne-Jones, Stanhope: A Text-Book of Bacteriology with a Section on Pathogenic Protozoa, ed. 7, New York, D. Appleton-Century Company, Inc., 1934, pp. 443-446. (*c*) Rake, G.: Studies on Meningococcus Infection: VI. The Carrier Problem, J. Exper. Med. **59:**553 (May) 1934. (*d*) Tillett, W. S., and Brown, T. M.: Epidemic Meningococcus Meningitis, Bull. Johns Hopkins Hosp. **57:**297 (Nov.) 1935.

may ultimately develop in carriers who have harbored meningococci for some time without symptoms.[10] Hence, it is reasonable to believe that meningococcic meningitis may appear in a carrier when fracture of the skull has created conditions suitable for invasion by the micro-organisms. That 3 of these cases were seen during the recent outbreak of meningococcic meningitis in New York [11] may be but a reflection of the presence of these micro-organisms in the nasopharynx in large numbers of the general population during epidemic periods.

In cases 1 to 3 the possibility is to be considered that the patient acquired the infection after admission to the hospital by contact with meningococcic carriers. Although there were no patients with meningococcic meningitis in the wards to which these patients were admitted, such patients were present in the other wards of the psychiatric medical service at the same time. This possibility, however, does not diminish the responsibility of the fracture of the skull in bringing about the meningitis. Although 30 cases of meningococcic meningitis have been observed in the wards of the psychiatric medical service of the Bellevue Hospital in the last eighteen months, no instance of contact infection of patients or hospital personnel has been observed. This is in accordance with the observations of others [12] on the extreme rarity of obvious infection from contact. However, in the recent outbreak in New York multiple cases of meningococcic meningitis were observed in 4 per cent of the families,[11] and in Baltimore [9d] a history of contact was noted in 7 of 21 cases.

It appears possible from the case reports already cited [13] that trauma may play a predisposing rôle in meningococcic meningitis without fracture of the skull. This receives some support from the experience of those who have observed the development of meningitis caused by the common pyogenic micro-organisms following trauma to the skull without fracture.[14]

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[10] MacCallum, W. G.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1932, pp. 536-537. Zinsser and Bayne-Jones.[9b]

[11] Bolduan, C., and Frant, S.: The Recent Increase in Meningococcus Meningitis, Quart. Bull. Dept. of Health, New York **4**:47, 1936.

[12] Simon, C. E.: Human Infection Carriers, Philadelphia, Lea & Febiger, 1919, pp. 106-133. Zinsser and Bayne-Jones.[9b]

[13] Footnotes 1, 2 and 5.

[14] (*a*) Weichselbaum, A., in Kolle, W., and Wassermann, A.: Handbuch der pathologenen Mikroorganismen, Jena, G. Fischer, 1903, vol. 3, p. 293. (*b*) Wechsler, I. S.: A Text-Book of Clinical Neurology, ed. 2, Philadelphia, W. B. Saunders Company, 1931, p. 370. (*c*) Finkelnburg, R.: Die Erkrankungen der Meningen, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 1091. (*d*) Ehrnrooth, E.: Eitrige Meningitis, akut entstanden nach Kopftrauma ohne nachweisbare Wunde, Deutsche Ztschr. f. d. ges. gerichtl. Med. **12**:30 (Aug. 27) 1928.

Although in our cases of meningococcic meningitis a potential communication between the meninges and the nasopharynx was created by the fracture of the sphenoid bone in case 2 and of the petrous portion of the temporal bone in cases 1, 3 and 4, it is not known that the micro-organisms traveled along this route. It is possible that trauma to the meninges and the brain furnishes an area of diminished resistance for micro-organisms invading directly from the nasopharynx or from the blood stream. In this connection, Ehrnrooth[14d] has shown in experimental animals that trauma to the head without fracture of the skull promotes the development of meningitis after the intravenous injection of micro-organisms. The rôle played in the propagation and dissemination of the meningococci by otitis and mastoiditis in case 3 and by hemorrhages in the sphenoid sinus in case 1 and in the middle ear in case 4 is not clear.

SUMMARY

Four cases are reported in which meningococcic meningitis followed fracture of the base of the skull. Attention is called to 16 similar cases reported in the literature, and the considerations are discussed which support the view that a direct causal relationship exists between fracture of the skull and meningococcic meningitis.

Drs. Thomas Gonzales, Benjamin Morgan Vance and Milton Helpern, of the Office of the Chief Medical Examiner, New York, supplied the necropsy records.

EFFECT OF STARVATION ON THE HEALING OF FRACTURES IN RABBITS

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Prolonged abstinence from foods providing certain essentials to normal life processes results in various well known deficiency diseases which must be distinguished from changes arising in normal animals suddenly deprived of all food intake. For purposes of clarity the former may be regarded as changes arising from chronic starvation and the latter as those arising from acute starvation. It is with healing in diseases arising from acute starvation that this paper is concerned.

A review of the literature reveals that investigators unanimously agree that acute starvation does not inhibit either growth or repair. McCollum and his co-workers[1] demonstrated that fasting would cause active rickets in rats to heal from within twenty-four to forty-eight hours. Shipley and Holt[2] reported studies in vitro and stated that solutions to which 51.3 millimols of sodium chloride had been added inhibited calcification in preparations of the bones of rats with rickets, while similar preparations from starved rats calcified perfectly. Harvey and his co-workers,[3] who studied the effect of starvation on fibroplasia and the healing of wounds in the stomach of the rat, found that starvation produced no change in the initiation of growth or in its velocity. Roegholt[4] found that lack of vitamin A did not slow up the processes of healing in a wound. Morgan[5] stated that the legs of starved salamanders regenerated after amputation as rapidly as those of normally fed animals.

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[1] McCollum, E. V.; Simmonds, N.; Shipley, P. G., and Park, E. A.: *The* Effect of Starvation on the Healing of Rickets, Bull. Johns Hopkins Hosp. **33**:31, 1922.

[2] Shipley, P. G., and Holt, L. E., Jr.: Effect of Starvation on Healing of Rickets in Rats, Proc. Soc. Exper. Biol. & Med. **25**:32, 1927.

[3] Howes, E. L.; Briggs, H.; Shea, R., and Harvey, S. C.: *Effect of* Complete and Partial Starvation on the Rate of Fibroplasia in the Healing *Wound*, Arch. Surg. **27**:846 (Nov.) 1933.

[4] Roegholt, M. N.: Influence of Diet Free from Vitamin A *on Myelopoiesis* and the White Blood Picture and Its Effect on Wound Healing, *Nederl. tijdschr. v. geneesk.* **2**:3744 (Aug. 10) 1929.

[5] Morgan, Thomas H.: The Physiology of Regeneration, *J. Exper. Zool.* **3**:457, 1906.

There is even some evidence that cell division is stimulated by starvation, as Morgulis and his co-workers[6] quoted Gaglio[7] as finding mitotic figures more frequent in tissues from starved than in those from normal frogs and Morpurgo[8] as finding the same for pigeons. Morgulis concluded from his studies that there is a reduction in cell cytoplasm in starved animals but little reduction in the nucleus. This disturbed ratio results in an increased rate of cell division in an effort to restore the proper balance. Harvey and his co-workers found in the rat that healing of well approximated clean wounds of soft parts is usually complete by fibroplasia in about fourteen days. However, healing of fractures involves more than repair by fibroplasia and requires a longer time. The callus that forms is at first fibrous and subsequently ossifies, partly by fibrous ossification and partly by enchondral ossification.

In order to test the effects of starvation on the phases of the healing of fractures, the following experiments were carried out.

EXPERIMENTAL WORK

Sixty-two adult rabbits of approximately the same age, weight and general physical condition were operated on, and the ulna was fractured by open operation about 1 inch (2.5 cm.) above the joint. No attempt at immobilization of the fracture was made. The animals were then divided into two groups. One group was fed the usual laboratory diet; the other group was placed in metabolism cages so that all excretions were immediately disposed of, and their intake was limited to a 0.9 per cent solution of sodium chloride. There was considerable variation in the ability of the animals to withstand starvation, as they succumbed at intervals ranging from nine to thirty-seven days. Control animals were killed at intervals corresponding in duration to those which succumbed to starvation. The specimens were dissected, roentgenograms were made and the specimens were then sectioned for microscopic examination.

RESULTS

RABBIT 745.—*Eighteen day fracture; normal diet.*

There was a large amount of external callus which was practically entirely ossified. Mesially both the radius and the ulna participated in the process of ossification. In the mesial external callus a large displaced fragment of cortex without nuclei was seen. New bone was being laid down on the dead fragment on two sides. Of the other two sides, the long side adjacent to the fibrous portion of the callus was without new bone, and the end in contact with the radius was necrotic and disintegrating, as was the contacting portion of the radius. The marked radial periosteal reaction ceased abruptly where contact with the dead fragment began. No cartilage was seen in the lateral external callus and only a small island in the mesial external callus. The fractured ends of the ulnar cortex were shredded and undergoing absorption, as evidenced by the large haversian canals.

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[6] (*a*) Morgulis, S.; Howes, P. E., and Hawk, P. B.: Studies on Tissues of Fasting Animals, Biol. Bull. **28**:397, 1915. (*b*) Morgulis, S.: Fasting and Undernutrition: A Biological and Sociological Study of Inanition, New York, E. P. Dutton & Company, 1923.

[7] Gaglio, G.: Sulle alterazioni istologiche e funzionali dei muscoli durante l'inanizione, Arch. per le sc. med. **7**:301, 1884; cited by Morgulis.[6b]

[8] Morpurgo, B.: Sull processo fisiologico di neoformazione callulare durante la inanizione acute dell' organismo, Arch. per le sc. med. **12**:395, 1888; cited by Morgulis.[6b]

The callus separating the opposing fragments of the ulnar cortex was ossified only in that region immediately surrounding the bone, leaving a wide strip of fibrous callus between the two ends. The medullary callus was a dense bony plate with a narrow unossified line in the center extending transversely across the medullary cavity. Numerous displaced spicules of cortical bone were present with new bone laid down on them. There was only a minimal amount of endosteal reaction present, it being most marked on the cortex next to the radius.

Rabbit 686.—*Eighteen day fracture; starvation.*

A thin line of lateral external callus was ossified except in the region of the fracture and a few millimeters of the adjacent cortex. Here there was a dense fibrous callus which separated the ends of the ulna and extended completely across the fracture defect. Disseminated throughout were spicules of cortical bone without nuclei and giant cells, some lying in contact with the dead bone.

There was no callus formation on the mesial side. In the interosseous region, between the ends of the fractured ulna and in the adjacent portion of the medullary cavity, was an acellular granular mass of necrotic tissue, representing the remains of an unabsorbed hematoma. The medullary callus was composed of a wide central band of moderately dense fibrous tissue with many large vacant spaces like those left where fat has been dissolved out during fixation. Peripherally, there were two bands of beginning ossification; the trabeculae here were thin and lacelike, and the cells were larger and closer together than those seen in the specimen from rabbit 745. There was a marked endosteal reaction present. The haversian canals of both the radius and the ulna were much larger than those in the specimen of rabbit 745, indicating osteoporosis.

Comment.—The specimen from the starved animal could be identified microscopically by the lesser amount of external callus, lack of ossification of both the external and the medullary callus, the spongy nature of the ossification present and the presence of osteoporosis.

Rabbit 737.—*Twenty-two day fracture; normal diet.*

The lateral external callus was ossified except for the region between the fragments of the fractured ulna. A small island of cartilage was attached to each of the fragments. The ossification of the mesial callus was limited to the few millimeters adjacent to the cortex of the radius and the ulna. The region immediately adjacent to the fracture line was cartilaginous, and between this cartilage and the fractured ulna were two small pieces of necrotic and disintegrating cortex. The fragments were in good alinement, and in the first few millimeters adjoining the fracture line no nuclei were seen. The region between the two ends contained a small amount of an acellular and granular material, representing an unabsorbed hematoma. On the medullary cavity side of the fracture line was a piece of necrotic disintegrating bone completely surrounded by a large island of cartilage and new bone which spanned the defect.

The medullary callus was ossified peripherally, forming two wide bands of dense bone which stretched transversely across the medullary space and were separated from one another by a narrow band of unossified callus, fibrous in the lateral half and cartilaginous in the mesial half. Spicules of displaced dead cortical bone with new bone laid down on them still remained. The endosteal reaction and ossification of the callus were more marked mesially than laterally.

RABBIT 681.—*Twenty-two day fracture; starvation.*

The lateral external callus was only partially ossified, being most marked in the cortical region of the proximal fragment. Mesially, ossification of the callus was occurring on the surface of both the radius and the ulna. There was a medullary callus at the site of the fracture which was cartilaginous in the intermediary zone and ossified distal to this in the ends of the fragments. It contained some spicules of dead bone that had been crushed into the cavity by the cutting forceps. Their cells had disappeared, and there was irregular formation of new bone on their surfaces.

Comment.—There was no doubt that both fractures were healing, but that healing was delayed in the starved animal was attested by a lack of ossification of the external callus, relatively less ossification of the medullary callus, lack of endosteal reaction and less actively appearing fibrous callus as compared with the specimen from the normal animal.

RABBIT 679.—*Twenty-nine day fracture; normal diet.*

The callus was completely ossified, forming a dense spongy plate of bone which united the fragments of the ulna. Between the fractured ends an acellular granular precipitate was seen, again representing the remainder of an unabsorbed hematoma. The cortices of the ends of the fragments were without nuclei for a short distance away from the fracture line. The periosteum of the radius in the neighborhood of the fracture had formed a layer of new bone.

The medullary callus was ossified except for one small island of cartilage. The ossified callus formed a wide plate of dense new bone composed of thick wavy trabeculae with small marrow spaces. In the meshes of this new bone lay numerous spicules of dead cortex undergoing bony transformation by creeping substitution.

RABBIT 683.—*Twenty-nine day fracture; starvation.*

The soft tissues attached along the lateral side were densely fibrous and included portions of tendons and muscle. That portion near the fracture line and in the periosteal regions was ossified. A large spicule of dead cortex lay out in the periphery of the lateral callus surrounded by dense fibrous tissue, except on one end. Here there was an island of cartilage with cartilage cells invading the dead spicule. The fragments of the ulna were dead for from 1 to 5 mm. away from the fracture line. A fibrous callus separated the fragments, ossification being limited to that portion immediately about the surface of the fracture.

There was no callus formation on the radial side. Here the fragments were in good alinement, and in the intervening space was a necrotic granular mass of tissue. The fragments were dead in the portions adjoining the fracture line and were undergoing absorption. The medullary callus was separated into two parts by a band of fatty marrow. That part associated with the lateral fragments of the ulna was composed of a central band of dense fibrous tissue continuous with the lateral callus and ossified peripherally where dead spicules of cortex were also being transformed. Here there was only a minimal amount of endosteal reaction. On the radial side a well marked endosteal reaction formed a hillock of new bone, which completely spanned the cortical defect. In the center of this hillock and spanning the fracture defect lay an island of cartilage. The ossification on the distal fragment was by spongy bone, and here there were many multinucleated giant cells. On the proximal fragment the bony trabeculae were heavier, and only a few giant cells were present.

Osteoporosis of the fragments of both the radius and the ulna was marked. The large number of giant cells present was an outstanding feature.

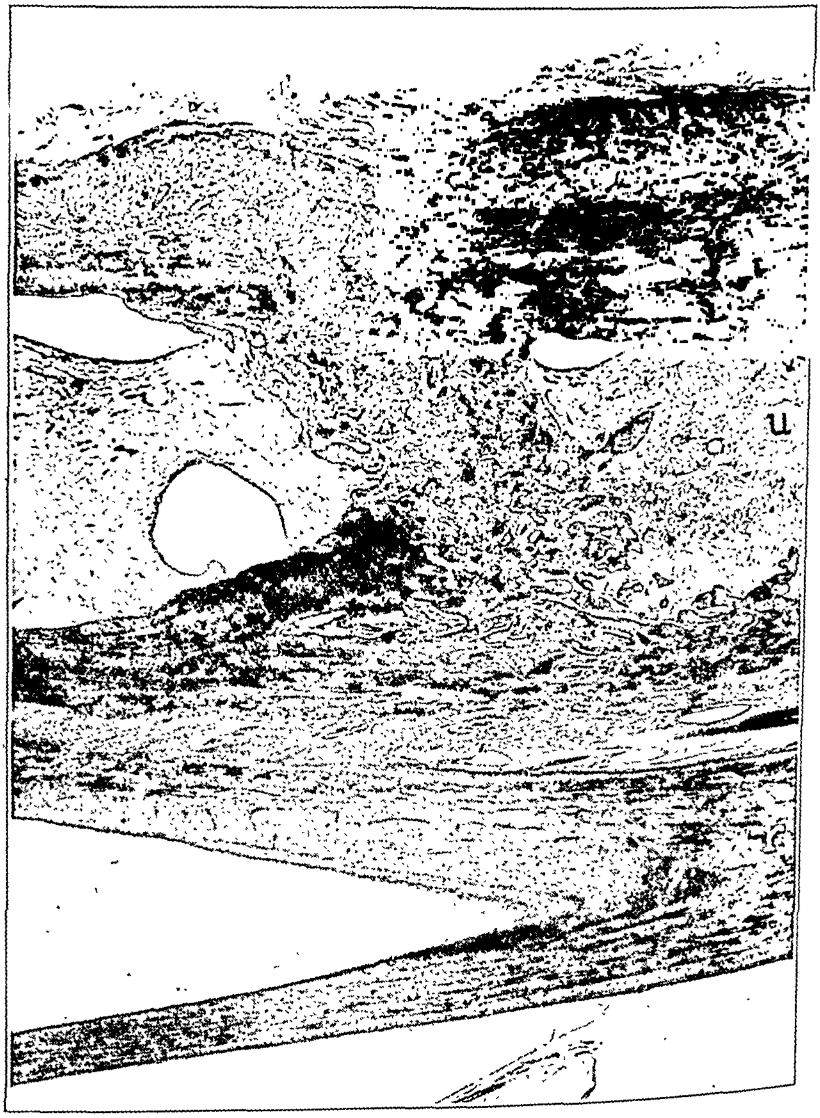

Fig. 1.—Section of a thirty-three day fracture of the ulna (*u*) of a rabbit on a normal diet. The callus is ossified. The radius is indicated by *r*.

Comment.—The specimen from the animal on a normal diet showed bony union, while that from the starved animal showed a callus that was partly ossified, and the bone was more spongy than that of the first specimen. The specimen from the starved animal showed marked osteoporosis.

RABBIT 239.—*Thirty-three day fracture; normal diet.*

A band of almost completely ossified callus united the fragments of the ulna and formed a wide bony bridge, which extended transversely across the medullary canal. A few cartilage cells were present in the intermediary callus. A few fragments of displaced cortical bone without nuclei lay scattered throughout this bony callus and were completely surrounded by living bone which had been deposited on them. The mesial cortex was united so well that if it were not for a large piece of dead cortical bone extending at an angle of 45 degrees into the medullary cavity and still attached at one end, one might doubt that a fracture had ever been present.

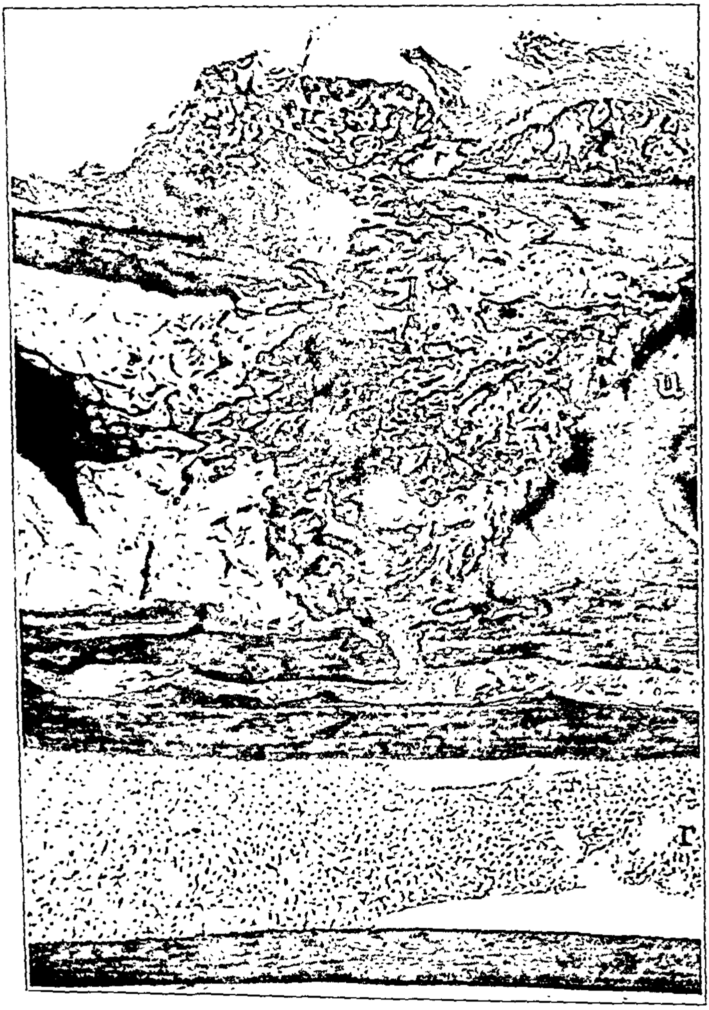

Fig. 2.—Section of a thirty-three day fracture of the ulna of a starved rabbit. The intermediary callus is fibrocartilaginous, and the bony callus is less dense than that in the control specimen (fig. 1). The ulnar (*u*) and radial (*r*) cortexes were osteoporotic.

Rabbit 321.—*Thirty-three day fracture; starvation.*

The lateral callus was ossified by a spongy type of bone. Between the ends of the fragments the fibrous callus remained unossified. There was no mesial callus formation, and the fragments here were not united, the intervening space being filled by tissue like the marrow elsewhere in the specimen. The ossification of the medullary callus was by a spongy type of bone, and extending transversely across the medullary cavity was a band of unossified callus composed about equally of fibrous tissue and cartilage. Marked osteoporosis was present. Giant cells and mononuclear cells were present in the dilated canals and along the surfaces of the cortex and also in the spongy bony callus, indicative of absorption of both the old and the new bone.

Comment.—These two specimens present a sharp contrast, revealing conclusively the inhibiting effect on bony union of acute starvation. The specimen from rabbit 239, the normal animal, shows a healed fracture; that from rabbit 321, the starved animal, shows an ununited fracture with the fracture line wide open, retarded ossification by a spongy bone and marked osteoporosis.

Rabbit 242.—*Thirty-four day fracture; normal diet.*

The ends of the fragments were united by densely ossified callus. The peripheral callus was small and roughly spindle shaped, and the medullary callus extended across the fracture line. It consisted of dense trabeculated bone, and there were a few giant cells and osteoblasts present, indicative of transformative activity.

Rabbit 246—*Thirty-four day fracture; starvation.*

The ends of the fragments were connected by an unossified callus. Practically no periosteal callus was present. The intermediary callus was largely fibrous and the remainder cartilaginous. The endosteal callus was limited in amount and consisted of spongy bone. Disseminated throughout the fibrous intermediary callus were spicules of dead cortical bone undergoing absorption and not associated with any new bone formation. Osteoporosis was again marked. The same absorptive activity of old and new bone by mononuclear and giant cells was seen as in the section from animal 321.

Comment.—Again the difference in the specimens is striking. The specimen from the normal animal showed bony union of the fracture; that from the starved animal showed marked delay in ossification of the callus and marked osteoporosis.

Rabbit 349.—*Thirty-seven day fracture; normal diet.*

The lateral cortex was comminuted. A large spicule of cortical bone without nuclei lay diagonally across the fractured region at an angle of about 35 degrees but united at both ends with the neighboring fragment. New bone was being deposited on it by creeping substitution. There was a completely ossified mesial external callus, and the periosteum of the radius had formed a layer of new bone in the region of the fracture. All that remained of the medullary callus were two long narrow strips of bone without nuclei. They resembled displaced cortical bone which had not been absorbed. The only remaining fibrous callus was in a small region just beneath the dead and angulated cortical fragment previously mentioned. The fracture line on the mesial side could be identified with difficulty.

Rabbit 347.—*Thirty-seven day fracture; starvation.*

The fracture on the radial side was united by a callus that was fairly extensive and consisted of spongy bone, except for two small regions of cartilage in the intermediary zones at the limits of a splinter. On the opposite side and in the region of the medulla the callus was fibrous in its intermediary portion. There was a thin layer of ossified endosteal callus bordering on the intermediary callus. The cortex of the ends of the fragments on this side had been extensively absorbed and partly replaced by new bone, and there was a thin layer of periosteal, spongy bony callus on the proximal fragment.

Comment.—The specimen from the normal animal was healed. That from the starved animal was united mesially by a spongy type of new bone, and laterally there was fibrous union. Ossification of medullary callus was only minimal and again chiefly in conjunction with displaced dead cortical spicules.

COMMENT

In normal adult animals the formation and the destruction of bone are in equilibrium. Fracture of a bone in such an animal, however, disturbs the equilibrium locally and causes a shift favoring the formation of bone. Fibroplasia appears in both the periosteal and the endosteal region and proceeds to the formation of a fibrous callus, which later ossifies. The histogenesis of the bone which forms as a result of both enchondral and membranous ossification of the newly formed fibrous callus is complex, for fibroblasts must undergo metaplasia into chondroblasts and osteoblasts, and some of the cartilage is replaced by invading new bone. Complete ossification of the callus eventually takes place.

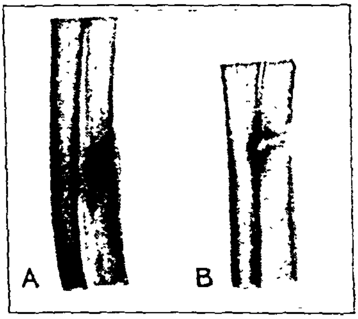

Fig. 3.—Roentgenograms of thirty-four day fractures of the ulna: *A*, a specimen from an animal on a normal diet, and *B*, a specimen from a starved animal.

Suppression of any one or all of these various phases would tend to reverse the equilibrium and thus result in retarded healing time or, if severe enough, lead to nonunion.

Fractures produced in the normally fed rabbits required between three and four weeks for complete ossification of the callus, whereas in none of the fractures in the starved animals was ossification complete, although eleven survived over four weeks. In fact, fractures in those animals which survived starvation more than thirty days showed less bony callus than did those from animals which succumbed to starvation in from twenty to twenty-six days.

One concludes, therefore, that acute starvation suppresses to some degree the process of ossification of the callus.

Comparison of the specimens from both starved and normally fed animals revealed no obvious difference in the time of appearance or completion of fibroplasia. Local factors, such as the amount of comminution, approximation of the fragments and disturbance of the periosteum, determine largely the amount of callus formed. Initiation and completion of fibroplasia and the amount of callus formed are therefore not affected by acute starvation. This observation agrees with that of Harvey and his co-workers, who could demonstrate no retarding effect of starvation on fibroplasia in well approximated clean wounds in soft tissue.

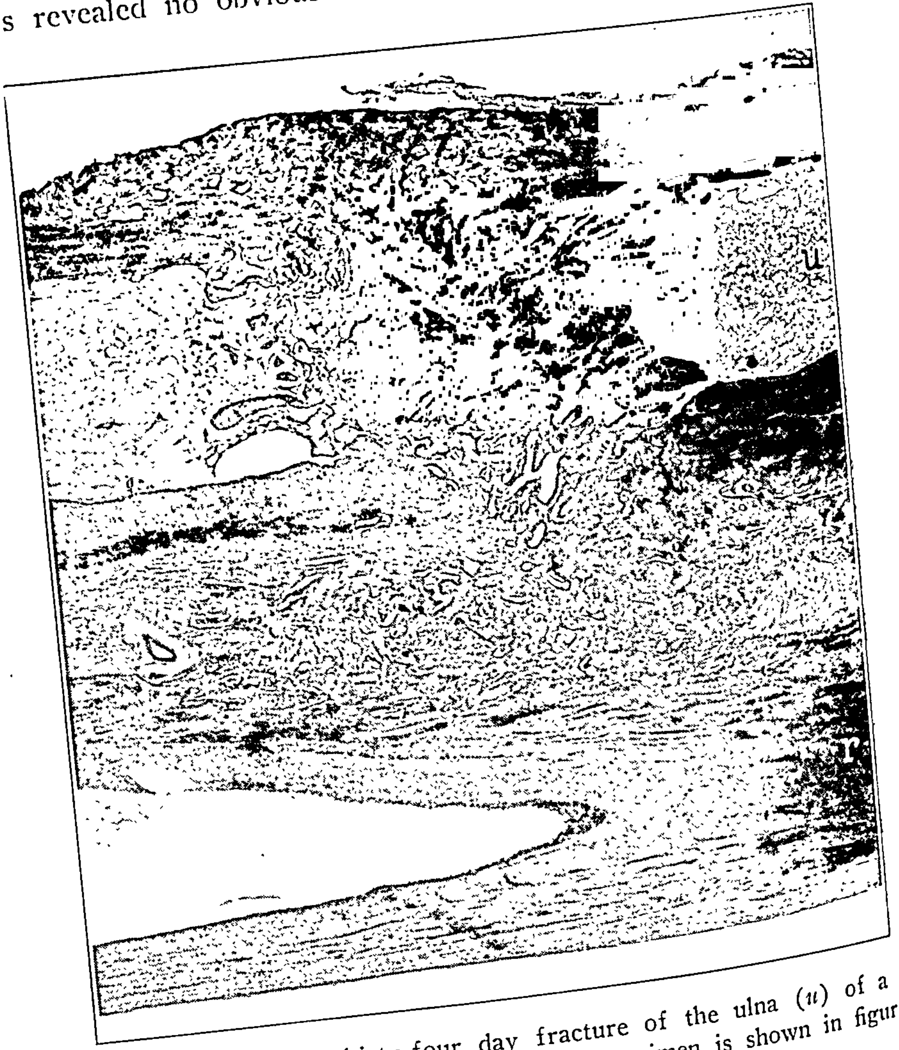

Fig. 4.—Section of a thirty-four day fracture of the ulna (*u*) of a rabbit on a normal diet. The roentgenogram of this specimen is shown in figure 3 *A*. The callus is ossified. The radius is indicated by *r*.

Starvation, then, must affect only the process of ossification. This may be accomplished in one or all of three ways, i. e.: by (1) inhibiting the metaplasia of fibroblasts into chondroblasts and osteoblasts; (2) by restricting the bone-forming activity of chondroblasts and osteoblasts to a minimum, or, since the retarding effect was proportional to the duration of the period of starvation, (3) by a shift of the equilibrium so as to accelerate the destruction of bone at the expense of the formation, in which case one would expect to see a preponderance of osteoclasts resulting in an absorption of the newly ossified callus and a generalized osteoporosis.

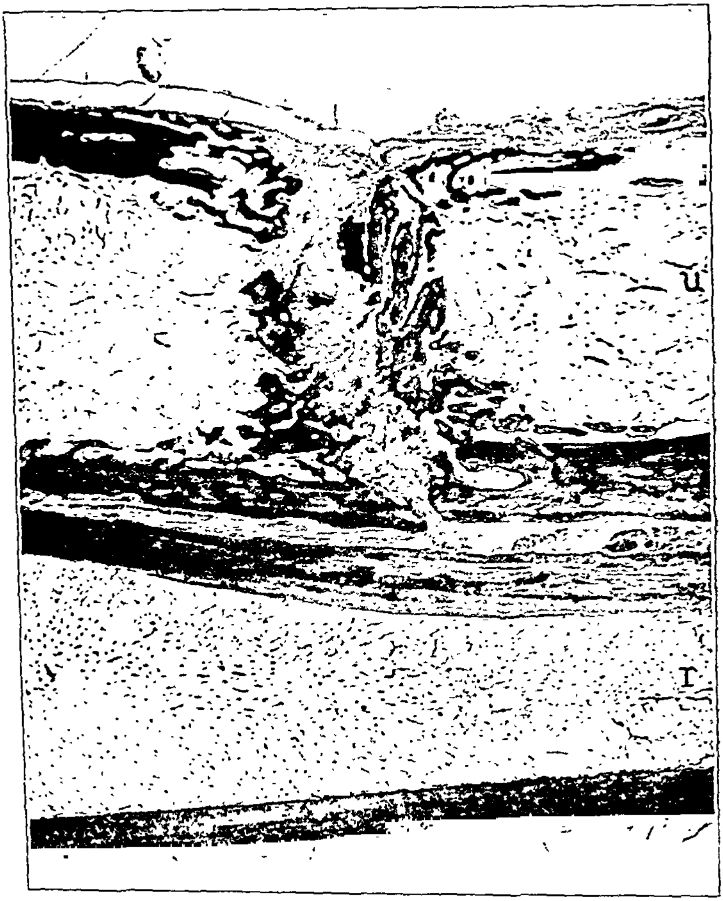

Fig. 5.—Section of a thirty-four day fracture of the ulna (*u*) of a starved rabbit. The roentgenogram of the specimen is shown in figure 3 *B*. The callus is smaller than that in the control specimen (fig. 4). The intermediary callus is fibrocartilaginous, and the bony callus is spongy. The ulnar cortex is markedly osteoporotic, and the radial cortex, less so.

Comparison of the specimens from starved and fed animals revealed that metaplasia had occurred in both, for both enchondral and membranous ossification were present. However, the older specimens from the starved animals could be distinguished from those from fed animals by (1) the relatively lesser amount of ossification and (2) the more spongy character of the bone that had been laid down. Generalized osteoporosis was present in the specimens from starved animals, almost from the beginning of ossification of the callus, but was much more marked in the specimens from animals which survived thirty days or more. In addition, the specimens from the latter actually exhibited many osteoclasts, lacunar absorption and less ossification than was seen in specimens from animals succumbing after from twenty to twenty-six days.

One can only surmise as to the actual mechanism of the retarding effect of starvation on ossification of the callus. It would seem, however, that in the beginning starvation chiefly inhibits metaplasia of the fibroblasts and limits the activity of the chondroblasts and osteoblasts to a minimum, so that healing progresses along a fairly normal but definitely inhibited course up to about twenty-six days. Thereafter the constantly increasing shift of equilibrium favoring the destruction of bone (as evidenced by the mild osteoporosis present) seems to be accelerated, osteoporosis increases and osteoclasts and lacunar absorption are seen in the ossified callus.

CONCLUSIONS

1. The healing of a fracture was definitely inhibited by starvation.

2. The process of healing was normal during the stage of the formation of a fibrous callus. But in animals that survived this stage there was definite retardation of ossification of the callus, which became more marked with an increase in the length of the survival period.

3. Generalized osteoporosis gradually developed, and in the animals that survived longest there was some osteoporosis in the callus that had previously ossified.

EFFECT OF ANESTHESIA ON THE BLOOD OXYGEN

II. A STUDY OF THE EFFECT OF SPINAL ANESTHESIA ON THE OXYGEN IN THE ARTERIAL AND IN THE VENOUS BLOOD

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In a preceding communication[1] the existence of anoxic anoxia during ether anesthesia was demonstrated. Spinal or subarachnoid anesthesia is used frequently in surgical procedures, and it is therefore desirable to investigate the effects of spinal anesthesia on the oxygen in the arterial and in the venous blood.

Seevers and Waters[2] stated that the oxygen content in the arterial and in the venous blood is lowered during spinal anesthesia. However, they used large enough doses of drugs to produce respiratory paralysis, which rarely occurs in clinical surgical procedures. They did not present any data to show the degree of change in the blood oxygen. On the other hand, Nowak noted no significant changes in the oxygen of the arterial blood of cats under spinal anesthesia.[3]

In the present investigation we have undertaken to confirm and extend the observations of the previous investigators on the oxygen in the arterial and in the venous blood during a surgical spinal anesthesia.

METHODS

Dogs were used. A lumbar laminectomy was performed two or three days previous to the experiment, to facilitate the performance of a subarachnoid injection of procaine hydrochloride. It was found after several trials of direct injection that this was the most certain method of obtaining spinal anesthesia.

From the Surgical Research Laboratory and the Fifth Surgical (Harvard) Service, the Boston City Hospital.

[1] Shaw, J. L.; Steele, B. F., and Lamb, C. A.: The Effect of Anesthesia on the Blood Oxygen: I. A Study of the Effect of Ether Anesthesia on the Arterial and Venous Blood Oxygen, to be published.

[2] Seevers, M. H., and Waters, R. M.: Respiratory and Circulatory Changes During Spinal Anesthesia, J. A. M. A. **99**:961 (Sept. 17) 1932.

[3] Nowak, S. J. G.: To be published.

The animal was placed in a supine position on the operating board. Under anesthesia with procaine hydrochloride the vena cava was catheterized via the external jugular vein, and the femoral artery was prepared as outlined in a previous communication.[1] After the animal was allowed to become perfectly quiet and adjusted to the surroundings, the pulse and respiratory rates and the blood pressure were recorded. The samples of arterial and of venous blood were taken from the femoral artery and the catheter in the vena cava, respectively.[1] The samples were drawn anaerobically, stored under liquid petrolatum and preserved in an ice bath while the oxygen determinations were being made. Potassium oxalate was used as an anticoagulant.

The animal was then turned on its left side and the laminectomy wound gently opened to expose the dura. This was done without causing the animal any apparent pain or distress. The dog's dura is extremely sensitive, and a puncture cannot be made without producing pain; so before a solution of procaine hydrochloride could be injected into the subdural space it was necessary to administer ethyl chloride for anesthesia for about twenty seconds. While the dog was under ethyl chloride anesthesia a solution of from 10 to 20 mg. of procaine hydrochloride per kilogram of body weight in 1 or 2 cc. physiologic solution of sodium chloride was injected into the subdural space by means of a small needle bent at a right angle. The solution was colored with a few drops of gentian violet in order to make any leakage detectable. Immediately after the injection the ethyl chloride was withdrawn and the animal allowed to recover from the anesthesia. This usually occurred in from sixty to ninety seconds. The animal was then turned back to the supine position. Anesthesia usually began immediately, and the level was noted by testing the skin with forceps or a sharp instrument.

Samples of arterial and of venous blood were taken, and the blood pressure and the pulse and respiratory rates determined after periods of thirty minutes and one hour, respectively. The animals were killed at the end of the experiment by quick intravenous injection of 100 mg. of sodium amytal per kilogram of body weight. Death occurred almost instantly. The trachea was exposed and clamped, and an immediate postmortem examination of the lungs was made.[4]

Blood oxygen determinations were made by the technic of Van Slyke and Neill.[4]

RESULTS

Eight experiments were performed. The results of the blood oxygen determinations for the experiments are recorded in tables 1 and 2 and shown graphically in charts 1 and 2.

The oxygen capacity of the arterial blood showed equivocal changes, though it tended to show changes of greater magnitude when decreasing.

In five of the eight experiments there was an increase in the oxygen content of the arterial blood. The greatest increase was 8.5 per cent. and the greatest decrease was 15.2 per cent. The mean change for the group was a slight increase.

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4. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

TABLE 1.—*Oxygen Values in Arterial and in Venous Blood of Dogs Under Spinal Anesthesia*

	Oxygen Capacity of Arterial Blood			Oxygen Content of Arterial Blood			Oxygen Content of Venous Blood			Arteriovenous Difference			Oxygen Saturation of Arterial Blood*			Oxygen Saturation of Venous Blood*		
		Blood Sample After Anesthesia			Blood Sample After Anesthesia			Blood Sample After Anesthesia			Blood Sample After Anesthesia			Blood Sample After Anesthesia			Blood Sample After Anesthesia	
	Control Blood	30 Min.	1 Hour	Control Blood	30 Min.	1 Hour	Control Blood	30 Min.	1 Hour	Control Blood	30 Min.	1 Hour	Control Blood	30 Min.	1 Hour	Control Blood	30 Min.	1 Hour
Experiment No.	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Volumes per Cent	Percentage	Percentage	Percentage	Percentage	Percentage	Percentage
2	24.9	26.1	26.2	23.0	25.2	24.6	17.1	18.6	17.4	5.9	6.6	7.4	92.4	95.5	91.6	68.8	70.5	66.4
3	16.0	15.5	15.4	13.4	13.9	14.3	8.8	4.8	3.8	4.6	9.1	10.5	84.0	89.7	92.9	55.0	30.9	24.7
5	17.7	16.7	17.2	16.2	16.0	15.9	11.1	7.9	8.2	5.1	8.1	7.7	91.5	95.8	92.4	62.7	47.3	47.6
6	22.6	23.6	22.8	21.1	21.4	20.9	10.7	12.2	11.5	10.4	9.2	9.4	93.5	90.7	91.7	47.5	51.8	50.4
7	20.8	17.9	17.6	19.0	16.8	16.1	15.6	6.9	5.9	3.4	9.9	10.2	91.3	93.8	91.5	75.0	38.7	33.5
8	19.7	17.4	17.7	17.9	17.3	17.2	12.0	4.3	9.6	5.9	13.0	7.6	90.4	99.4	97.2	61.0	24.6	54.3
10	16.2	16.5	16.6	14.4	15.0	14.5	9.8	8.0	...	4.6	7.0	...	88.9	90.7	87.3	60.5	48.5	....
11	13.9	14.4	14.1	12.8	13.8	13.9	9.2	7.2	7.6	3.6	6.6	6.3	92.2	95.8	98.5	66.2	50.0	53.0
Mean percentile change for the experimental series		−2.31	−2.71		+1.31	+0.47		−28.14	−26.65		+78.12	+75.92		+3.47	+2.83		−16.7	−15.05
Mean variation of the mean percentile change †		±4.39	±5.69		±5.78	±7.44		±19.50	±21.30		±50.28	±58.75		±2.35	±3.00		±13.17	±14.51
Mean of the mean variation of the mean percentile change		±1.55	±2.01		±2.05	±2.63		± 6.89	± 7.53		±22.43	±20.70		±0.83	±1.21		± 4.65	± 5.14

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* In the computation of the oxygen saturation of the arterial and venous blood, 0.5 and 0.3 volumes per cent were deducted from the oxygen capacity of the arterial blood and the oxygen content of the arterial and venous blood, respectively, to correct for the dissolved oxygen not in combination with the hemoglobin. The oxygen capacity of the arterial blood was used to calculate the oxygen saturation of the venous blood for general comparison, since the venous oxygen capacity of the venous blood was not ascertained in all instances.

† Scott, E. L.: What Constitutes an Adequate Series of Physiological Observations? J. Biol. Chem. **73**: 81, 1927.

In seven of the eight experiments there was a decrease in the oxygen content of the venous blood, the greatest decrease being 64 per cent. In one experiment there was an increase of 14 per cent in the oxygen content.

The arteriovenous difference increased sharply in seven of the eight experiments. In the one experiment in which no increase was recorded the initial arteriovenous difference was abnormally high.

In seven of the eight experiments an increase in the oxygen saturation of the arterial blood was noted. The greatest increase noted was 9 per cent and the smallest 0.4 per cent. In a single experiment a decrease in saturation of 2.8 per cent was recorded.

Table 2.—*Oxygen Values in Blood Samples Taken from Different Regions of the Body* (Experiment 8)*

Time of Taking Blood Sample	Blood Oxygen	Site of Blood Sample: Femoral Artery	Right Side of Heart†	Femoral Vein	External Jugular Vein
Control	Content (volumes per cent).......	17.9	12.0	11.1	12.4
	Capacity (volumes per cent)......	19.7	20.3		
	Percentage of saturation..........	91.0	61.0	56.4	62.8
30 minutes	Content (volumes per cent).......	17.3	4.3	8.2	7.9
	Capacity (volumes per cent)......	17.4	18.6		
	Percentage of saturation..........	99.7	24.6	47.4	45.7
1 hour	Content (volumes per cent).......	17.2	9.6	10.0	8.9
	Capacity (volumes per cent)......	17.7	19.1		
	Percentage of saturation..........	97.7	54.3	56.4	50.5

* The oxygen capacity of the arterial blood was used in computing the oxygen saturation of the venous blood for general comparison, since oxygen capacity of the venous blood was not determined in all the experiments.

† This sample of blood was taken from the junction of the superior and the inferior vena cava, as outlined under "Methods." It is not truly blood from the right side of the heart, but for practical purposes it should be almost identical.

In six of the eight experiments there was a decrease in the oxygen saturation of the venous blood. In two experiments small increases in the oxygen saturation were recorded, the largest of which was 4.3 per cent.

Table 2 shows the values for the samples of blood taken from different sources. The blood from the anesthetized area shows a slightly higher oxygen content than that taken from the upper part of the body. The difference is not marked and is well within the range of experimental variation.

There was no change in the blood pressure in experiment 5. In experiment 7 there was an increase in the blood pressure of 5.6 and 7.5 per cent for the thirty minute and one hour periods, respectively. Changes in the blood occurred in these experiments in spite of the failure of the blood pressure to drop. The average changes for the five experiments were 37.5 and 31.1 per cent for the thirty minute and one hour periods, respectively. The lowest blood pressure reached was 40 mm. of mercury, a decrease of 71 per cent from the control.

The respiratory rate showed equivocal changes, though it tended to increase slightly and usually became shallower and largely diaphragmatic.

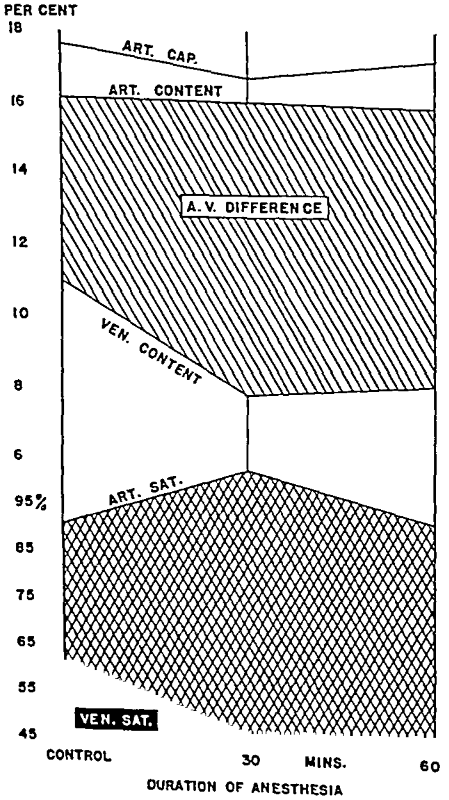

Chart 1

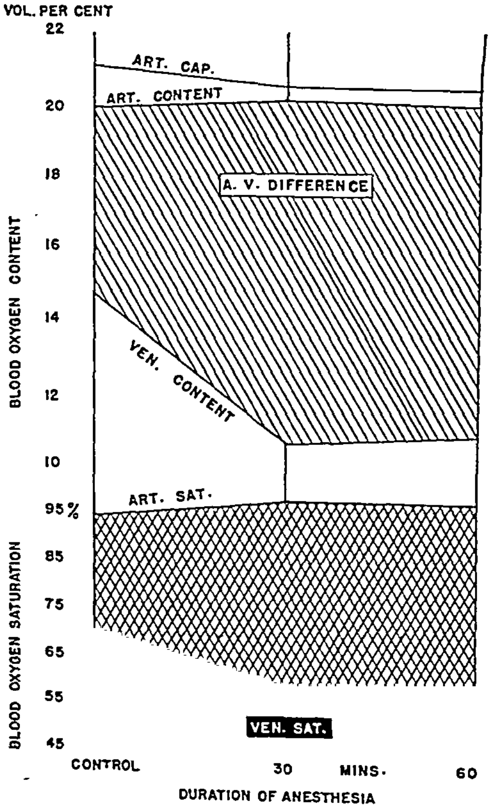

Chart 2

Chart 1.—Blood oxygen determinations in experiment 5.

Chart 2.—Mean of the results of the experimental series. The values used in this chart were calculated by use of the mean percentile changes for the experimental series, and as the control the following normal values for human blood were used: oxygen capacity of the arterial blood, 20.9 volumes per cent; oxygen content of the arterial blood, 19.9 volumes per cent; oxygen content of the venous blood, 14.9 volumes per cent; arteriovenous difference, 5 volumes per cent; oxygen saturation of arterial blood, 95 per cent, and oxygen saturation of venous blood, 71.4 per cent.

On postmortem examination the lungs appeared well inflated and evenly colored, except for a few small areas in the most dependent portions of the bases of the lungs, which were bright red. The striking feature about the lungs was their unusual paleness—a whitish pink—as if they were almost drained of their normal blood content. Removal of the tracheal clamp allowed the lungs to collapse without any areas of diminished crepitation. Gross section showed nothing remarkable, and no fluid could be expressed from the cut surface. The results of the microscopic examination were negative except for sparsely filled capillaries.

COMMENT

It is apparent that spinal anesthesia in the dog produces the following changes:

1. An increase in the oxygen saturation of the arterial blood. This change may be explained by the finding of a diminished content of the pulmonary blood, as indicated by the postmortem paleness of the lungs and a prolonged time for circulation of pulmonary blood.[5] The diminished flow of pulmonary blood plus the exposure of a smaller quantity of blood than normal to the entire capillary-alveolar bed of the lungs insures the complete oxygenation of the arterial blood.

2. A decrease in the oxygen content of venous blood. This change is due to stasis and is found in such conditions as shock[6] and cardiac decompensation. The blood from the right side of the heart may be considered as coming from two sources: the upper, unanesthetized, and the lower, anesthetized, area of the body. Its blood content will be the resultant of the mixture of blood from these two sources. Determinations on the oxygen in blood specimens taken simultaneously from each area of the body should give the source of the stasis. The results in experiment 8, shown in table 2, demonstrate that stasis occurs in both these regions of the body and appears to be slightly greater in the upper, unanesthetized, portion. The low oxygen content of venous blood in the upper, unanesthetized, part of the body is due to the reduced blood flow resulting from a compensatory vasoconstriction necessary to maintain a normal blood pressure. In conformity with the conception of an increased flow of blood through the anesthetized portion of the body due to the vasodilatation from vasoconstrictor

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[5] Nowak, S. J. G.: Personal communication to the authors. Shaw, J. L.; Steele, B. F., and Lamb, C. A.: Unpublished data on dogs using the sodium cyanide method.

[6] Aub, J. C., and Cunningham, T. D.: Studies in Experimental Traumatic Shock: II. The Oxygen Content of the Blood, Am. J. Physiol. 54:408, 1920-1921.

paralysis,[7] it would be expected that the oxygen content of the venous blood would be normal or elevated. On the contrary, it was observed to be lowered. The vasodilatation in the anesthetized area of the body, unlike the arteriolar dilatation seen when ether anesthesia is used,[8] involves the arterioles, capillaries and venules as a result of complete paralysis of their innervation. Since Krogh[9] has shown that under normal circumstances only a small proportion of the capillaries are used at any one time, this vasodilatation, assisted by the paralysis of the voluntary muscles, enlarges the vascular bed and results in the shifting or pooling of part of the blood volume in the anesthetized part of the body. Bradshaw[10] has shown that this vasoconstrictor paralysis is responsible for the fall in blood pressure observed in spinal anesthesia. Burch and Harrison[11] have demonstrated that as a sequel to a fall of 30 per cent or more in blood pressure the return of venous blood to the right side of the heart becomes inadequate, and a decreased cardiac output follows.

It is evident in the animals showing a fall in blood pressure that the pooling of blood from the vasodilatation in the region of anesthesia plus a diminished cardiac output and lowered blood pressure may produce a stasis of sufficient magnitude to explain the low oxygen content of the venous blood. The pale, blanched-appearing lungs may be further evidence of poor venous return to the heart from peripheral pooling.

The findings in the blood from the right side of the heart in the two experiments in which there was an increase and no change, respectively, in the blood pressure could be explained by a generalized vasoconstriction.[12] However, that would be expected to elevate the blood pressure more than the observed 7.5 per cent. Since a flaccid paralysis of voluntary muscles occurred in all instances, the blood pressure may have been maintained either by an adequate vasoconstriction in the unanesthetized area of the body or by a partial generalized vasoconstriction in the anesthetized part of the body. In the two experiments in which there was no change in the blood pressure it may be that the vasodilatation opens up such a vast additional capillary bed through which the blood flow is distributed that, in spite of an adequate blood pressure, the volume of flow through any one channel is diminished. Since the tissue metabolism is not hindered as in ether anesthesia,[13] the oxygen is removed in a greater than normal quantity during this paradoxical stasis. This may not be in accord with the finding of an elevated oxygen content of the venous blood in sympathectomized animals.[14] However, in these animals there had been time for some compensation from the acute vasodilatation, and normal muscular tone and function were present to aid in the movement of blood toward the heart.

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[7] White, J. C.: Diagnostic Novacaine Block of the Sensory and Sympathetic Nerves: Method of Estimating Results Which Can Be Obtained by Their Permanent Interruption, Am. J. Surg. **9**:264, 1930. Morton, J. J., and Scott, W. J. M.: The Measurement of Sympathetic Vasoconstrictor Activity in the Lower Extremities, J. Clin. Investigation **9**:235, 1930. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to the Extremities with Procaine: Test to Evaluate the Benefit of Sympathetic Ganglionectomy, J. A. M. A. **94**:1382 (May 3) 1930. Burch, J. C., and Harrison, T. R.: The Effect of Spinal Anesthesia on Arterial Tone, Arch. Surg. **22**:1040 (June) 1931.

[8] Embley, E. H.: Action of Ether upon the Circulation, Biochem. J. **4**:79, 1910.

[9] Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1922.

[10] Bradshaw, H. H.: The Fall in Blood Pressure During Spinal Anesthesia, Ann. Surg. **104**:41, 1936.

[11] Burch, J. C., and Harrison, T. R.: Effect of Spinal Anesthesia on Cardiac Output, Arch. Surg. **21**:330 (Aug.) 1930.

3. An increase in the arteriovenous difference. This is the consequence of the lowered oxygen content of the venous blood.

4. Stagnant anoxia. The findings of a perfectly saturated arterial blood and a lowered oxygen content of the venous blood, or an increased arteriovenous difference, are typical of a stagnant anoxia.[15] The stagnant anoxia of spinal anesthesia differs from the anoxic anoxia of ether anesthesia in that the blood oxygen reaches the tissues at an adequate available tension but in an insufficient quantity for the requirements of the tissue metabolism. The results indicate that the stagnant anoxia is general and will vary in degree with the extent of the area anesthetized or the magnitude of the vasoconstrictor paralysis and vasomotor compensation. The significance of anoxia in surgical anesthesia has been discussed in a previous communication.[1]

SUMMARY

Spinal anesthesia in dogs causes the following changes: (*1*) an increase in the oxygen saturation of the arterial blood, a decrease in the oxygen content and saturation of the venous blood, and an increase in the arteriovenous oxygen difference and (2) pale, blanched-appearing lungs, possibly indicating incompletely filled lung capillaries.

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[13] Brow, G. R., and Long, C. N. H.: Biochemical Changes in the Heart During Anesthesia, Anesth. & Analg. **9**:193, 1930.

[14] Freeman, N. E.: Personal communication to the authors.

[15] Barcroft, J.: Anoxaemia, Lancet **2**:485 (Sept. 4) 1920.

CONCLUSION

The foregoing changes indicate the existence of a stagnant anoxia. It is suggested that the anoxia may be minimized by the use of small doses of the anesthetizing drug or by controlling the administration in such a way as to involve a minimum number of the sympathetic vasoconstrictor fibers and employing vasoconstricting drugs which act principally on the capillary walls.

EXPERIMENTAL CEREBRAL TRAUMA

THE FLUID CONTENT OF THE BRAIN AFTER TRAUMA TO THE HEAD

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On no subject is there greater divergence of opinion than on the proper methods of treatment of injuries of the head with their resultant cerebral damage. Fay[1] advocated an extreme degree of dehydration by the use of hypertonic solutions, both intravenously and by bowel, and rigid restriction of the fluid intake; Munro[2] advised reduction of pressure and removal of blood by frequent spinal punctures; Sachs[3] expressed the opinion that spinal puncture is dangerous and contraindicated, and Dandy[4] advised against the use of both hypertonic solutions and spinal puncture, preferring operative decompression in cases in which there is evidence of a high increase in the intracranial pressure.

The reason for the contradictory nature of these opinions is not difficult to find. It is based on ignorance of the mechanism of the cerebral damage attending injuries of the head. The literature abounds with postmortem statistics and clinical opinions which attribute the cause of symptoms following injuries to the head to petechial hemorrhage, molecular displacement, edema (both local and general), "traumatic hydrocephalus" and other hypothetic disorders. But there is little positive proof of the existence of any of them.

Adequate experimental studies on the subject are meager. In 1894 Halliburton[5] first called attention to the physiologic significance of the

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[1] Fay, T.: Head Injuries: Result Obtained with Dehydration in Forty-Eight Consecutive Cases, J. Iowa M. Soc. **20**:447, 1930; Generalized Pressure Atrophy of the Brain, Secondary to Traumatic and Pathologic Involvement of Pacchionian Bodies, J. A. M. A. **94**:245 (Jan. 25) 1930; The Treatment of Acute and Chronic Cases of Cerebral Trauma, by Methods of Dehydration, Ann. Surg. **101**:76, 1935.

[2] Munro, D.: The Diagnosis, Treatment and Immediate Prognosis of Cerebral Trauma: An Introductory Study of 1,494 Cases, New England J. Med. **210**:287 (Feb. 8) 1934; The Therapeutic Value of Lumbar Puncture in the Treatment of Cranial and Intracranial Injury, Boston M. & S. J. **193**:1187 (Dec. 24) 1925.

[3] Sachs, E.: The Diagnosis and Treatment of Head Injuries, J. A. M. A. **81**:2159 (Dec. 29) 1923; Head Injuries, Internat. J. Med. & Surg. **46**:567, 1933.

[4] Dandy, W. E.: Diagnosis and Treatment of Injuries of the Head, J. A. M. A. **101**:772 (Sept. 2) 1933.

[5] Halliburton, W. D.: The Proteids of the Nervous System, J. Physiol. **15**:90, 1894.

fluid content of the brain and pointed out the marked difference between the gray and the white matter in this respect. His findings and conclusions were reiterated in a later paper.[6] In studies on the brains of men, monkeys, dogs and cats he found the average fluid content of the normal gray matter to be 83.5 per cent, and that of the white matter, 69.9 per cent. In 1896 there appeared a monograph by Leonard Hill on "The Cerebral Circulation,"[7] in which he identified cerebral edema as fluid squeezed out of capillaries by some already existing cerebral compression. Shortly thereafter, Courtney[8] suggested that a vasomotor paralysis resulting from the original injury to the head gave rise to arteriolar dilatation and subsequently to edema. In 1901 Cannon[9] summarized existing opinions and reported experiments on trauma to the head, adding hypothetic anemia and osmotic changes to the possible causes of cerebral edema. Liesegang and Mayr[10] in 1912 attributed cerebral edema to accumulation of acid resulting from anemia of the brain.

In these early papers and in nearly all subsequent studies edema of the brain has been assumed to be the principal compressing factor in those cases of injury to the head in which there was no gross hemorrhage or major bony depressions. Some authors, particularly in France and Germany, have postulated the existence of local edema about the third ventricle (Arnaud[11]), the aqueduct (Denis,[12] Karitzky[13]) or the outlet of the fourth ventricle (Hauptmann[14]), with a resulting obstructive hydrocephalus.

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6. Halliburton, W. D.: Die Biochemie der peripheren Nerven, Ergebn. d. Physiol. **4**:23, 1905.

7. Hill, L.: The Physiology and Pathology of the Cerebral Circulation, London, J. & A. Churchill, 1896.

8. Courtney, J. W.: Traumatic Cerebral Edema: Its Pathology and Surgical Treatment; a Critical Study, Boston M. & S. J. **140**:345, 373 and 397, 1899: quoted by Cannon.[9b]

9. Cannon, W. B.: (*a*) Intracranial Pressure After Head Injuries, Boston M. & S. J. **145**:158, 1901; (*b*) Cerebral Pressure Following Trauma, Am. J. Physiol. **6**:91, 1901-1902.

10. Liesegang, R., and Mayr, E.: Hirnschwellung: I. Die Physik und Chemie der Hirnschwellung, Ergebn. d. Neurol. u. Psychiat. **2**:157, 1912.

11. Arnaud, M.: Recherches sur les hypertensions intracraniennes bloquées du liquide céphalo-rachidien consécutives aux traumatismes craniens, et en particulier sur les hypertensions intraventriculaires, Bull. et mém. Soc. nat. de chir. **59**:843 (June 3) 1933.

12. Denis, R.: Au sujet du traitement des lésions traumatiques cranio-encéphaliques, J. de chir. **42**:873, 1933.

13. Karitzky, B.: Hirndruck bei stumpfen Kopfverletzungen, Deutsche Ztschr. f. Chir. **242**:1, 1933.

14. Hauptmann: Die Objektivierung postcommotioneller Beschwerden durch das Encephalogramm, Zentralbl. f. d. ges. Neurol. u. Psychiat. **48**:846, 1927-1928.

Most of the meager experimental studies on the subject of cerebral edema are subject to various criticisms. Apfelbach [15] determined the fluid content of blocks of traumatized brains removed at autopsy but apparently did not separate the gray from the white matter or determine the proportions of each in the blocks. Since the gray and the white matter may differ 10 per cent or more in their water contents, Apfelbach's values cannot be considered significant. The same objection applies to studies on heat stroke by McKenzie and LeCount,[16] as does also the objection that the studies were made at varying and often long intervals after death. The dogs' brains studied by Masserman and Schaller [17] were dried only twenty-four hours at an unstated temperature. Histologic evidence of edema of the brain (Winkelman and Eckel,[18] Masserman and Schaller,[17] Rand and Courville [19] and Hoff [20]) cannot be considered conclusive on account of the many variable factors in the preparation of the material, such as fixation, dehydration, cutting and staining.

There have been no direct experimental studies on the fluid contents of traumatized brains. This fact, as well as many other shortcomings in existing knowledge of the mechanism of injuries to the head, has been recently emphasized in the comprehensive and critically written review of Lehman and Parker.[21] The reader is referred to this paper and to those of Masserman [22] and Winkelman and Eckel [18] for detailed bibliographies.

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15. Apfelbach, C. W.: Studies in Traumatic Fractures of the Cranial Bones: I. Edema of the Brain; II. Bruises of the Brain, Arch. Surg. **4**:434 (March) 1922.

16. McKenzie, P., and LeCount, E. R.: Heat Stroke, with a Second Study of Cerebral Edema, J. A. M. A. **71**:260 (July 27) 1918.

17. Masserman, J. H., and Schaller, W. F.: Intracranial Hydrodynamics: II. Influence of Rapid Decompression of the Ventriculosubarachnoid Spaces on the Occurrence of Edema of the Brain, Arch. Neurol. & Psychiat. **30**:107 (July) 1933.

18. Winkelman, N. W., and Eckel, J. L.: Brain Trauma: Histopathology During the Early Stages, Arch. Neurol. & Psychiat. **31**:956 (May) 1934.

19. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: Reaction of Microglia and Oligodendroglia, Arch. Neurol. & Psychiat. **27**:605 (March) 1932.

20. Hoff, H.: Experimentelle Studien zur Frage des postkommotionellen Hirnödems, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:583, 1930.

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22. Masserman, J. H.: Intracranial Hydrodynamics: Central Nervous System Shock and Edema Following Rapid Fluid Decompression of the Ventriculo-Subarachnoid Spaces, J. Nerv. & Ment. Dis. **80**:138, 1934; Cerebrospinal Hydrodynamics: IV. Clinical Experimental Studies, Arch. Neurol. & Psychiat. **32**:523 (Sept.) 1934. Masserman and Schaller.[17]

The experiments to be reported herein were designed to determine the effect of trauma to the head on the fluid content of various portions of the brain and on the volume outflow of cerebrospinal fluid. In other experiments the effect of the intravenous administration of hypertonic solution of dextrose in traumatized animals was determined.

METHODS AND RESULTS

All of the sixty experiments were performed on dogs weighing from 7 to 12 Kg. The animals were anesthetized with sodium barbital, 0.3 Gm. per kilogram of body weight, administered intravenously at least two hours before the beginning of the experiments. The animal's head was held rigidly in a constant position throughout the experiment. Cerebrospinal fluid pressure was determined by means of a needle in the cisterna magna connected with a water manometer. Arterial blood pressure was recorded by means of a cannula in the femoral artery.

Measured trauma was administered to the head by dropping a standard 500 or 1,000 Gm. metal weight on the vertex of the head from a constant height of 60 inches (154 cm.). In each experiment the weight was dropped twice in rapid succession.

After the conclusion of one of the various types of procedure to be described, each experiment was terminated by stabbing the heart. The brain was immediately removed (requiring seven minutes or less), and specimens of gray and of white matter from the cerebral cortex and of gray matter from the cerebellum and a portion of the medulla and pons were quickly separated, placed in weighing bottles or beakers and weighed. Gray matter and white matter were separated by a standard rapid technic, by means of which a minimum of one type of tissue was left clinging to the specimen of the other. A sharp knife was used, and great care was exercised to avoid compressing or macerating the specimens. The constancy of the findings to be related attests the accuracy of the separation.

Specimens were dried to constant weight in an oven at 60 C. (usually requiring four or five days), and their fluid and solid contents were thus determined.

Some animals showed extravasation of blood into the scalp or temporal muscle, and an occasional small laceration of the scalp was produced, but in no instance was either fracture of the skull or perceptible intracranial hemorrhage produced by the trauma. One animal died five minutes after the trauma without showing elevation of the cerebrospinal fluid pressure or of the blood pressure. In this dog the fluid contents of the several specimens from the brain were within the normal range. The results of this experiment are not included in the tables.

In the normal dog, with the head in the position used throughout these experiments, the cerebrospinal fluid usually rose to the top of the needle and occasionally dripped out slowly. It did not rise sufficiently high to become visible in the manometer, to which the needle was attached by an adapter and a short rubber tube. The distance from the needle to the zero point of the manometer was 2 cm. The pressure was considered normal when the fluid was not visible in the manometer, and this normal pressure is designated in the tables by the symbol ±. This degree of pressure (±) was observed in all animals before the infliction of the trauma.

The various types of experiments will be considered separately, and average findings in all groups of dogs will later appear in the composite table 7.

Group 1.—*Normal Controls.*—Five dogs were killed twelve hours after receiving the usual dose of barbital and being kept in the same position as the animals in the remaining experiments. Table 1 shows the fluid contents of the portions of their brains examined. The relatively narrow limits of variation are clearly shown. The values found correspond closely to those found by Calhoun and myself[23] by the same method in twenty-four laboratory dogs which had been previously used for various experiments not involving the nervous system. In three of these animals the cerebrospinal fluid pressure was observed throughout the experiments and was never found to rise above the normal level. Similarly, the mean blood pressure maintained a rather constant level, tending to fall slightly after about eight hours.

Table 1.—*Percentage of Water in the Brains of Normal Dogs Anesthetized with Sodium Barbital*

Dog No.	Fluid in Cerebral Gray Matter, %	Fluid in Cerebral White Matter, %	Fluid in Cerebellar Gray Matter, %	Fluid in Medulla Oblongata, %
T7	79.9	68.8	79.8	70.4
T14	79.8	67.0	80.0	70.2
T24	79.2	68.2	79.6	70.8
T44	78.3	68.8	79.7	71.9
T45	79.8	67.4	79.2	71.1
Averages	79.4	68.0	79.6	70.9

Table 2.—*Fluid Content of the Brains of Dogs Killed at Arbitrary Intervals After Trauma by a 500 Gm. Weight*

				Cerebrospinal Fluid Pressure					
Dog No.	Time Dog Was Killed, Hours After Trauma	Immediate Rise in Mean Blood Pressure, Mm. of Hg	Later Rise in Mean Blood Pressure, Mm. of Hg	Maximum Increase, Mm. of H_2O	Increase at End of Experiment, Mm. of H_2O	Fluid in Cerebral Gray Matter, %	Fluid in Cerebral White Matter, %	Fluid in Cerebellar Gray Matter, %	Fluid in Medulla Oblongata, %
T1	2	0	0	±	±	82.3	71.0	82.2	74.0
T2	2	5	20	30	30	79.8	69.5	80.5	70.0
T3	2	10	0	20	20	79.5	67.8	80.1	70.0
T4	2	8	0	±	±	79.7	66.0	80.1	69.3
T5	2	0	0	±	±	79.3	68.5	80.3	71.6
T6	4	3	10	35	35	81.0	68.8	80.7	71.2
T51	4	6	10	30	±	79.4	68.2	80.5	70.1
T8	8	0	14	40	±	80.8	70.6	81.2	71.8
T9	8	0	8	20	10	80.1	70.4	80.9	70.2
T10	24	0	0	10	±	79.7	69.5	80.5	70.5
T54	24	0	10	25	5	79.9	69.8	80.4	70.6
T56	24	4	16	35	20	79.5	69.6	80.2	70.2
Average						80.1	69.1	80.6	70.8

Group 2.—*Trauma by a 500 Gm. Weight; Animals Killed After Various Intervals.*—Five of the animals in this group were killed two hours after trauma, and two were killed four hours, two eight hours and three twenty-four hours after trauma. The results are shown in table 2.

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[23] Pilcher, C., and Calhoun, J. A.: Unpublished observations.

An increase in the cerebrospinal fluid pressure within two hours was produced in only two of the five dogs, and the increase in pressure did not exceed 40 mm. of water in any of the twelve animals. A typical curve of cerebrospinal fluid pressure after this degree of trauma is shown in chart 1.

Changes in blood pressure were not marked in any animals of this group.

The fluid content of the various portions of the brain showed small variations in individual instances, but the average values indicate a small but definite increase in the fluid content of the cerebral and the cerebellar gray matter, beginning two hours after the trauma and increasing until the eight hour period, followed by a return close to the average normal level at the end of twenty-four hours. On the other hand, the average fluid content of the white matter and the medulla did not show a significant increase until eight hours after trauma. This increase persisted for twenty-four hours in the cerebral white matter but not in the medulla. The average increases observed in the fluid content were very small, the greatest alteration being an average increase of 1.5 per cent in the cerebral white matter after eight hours. The possible significance of changes of this low order of magnitude will be discussed later.

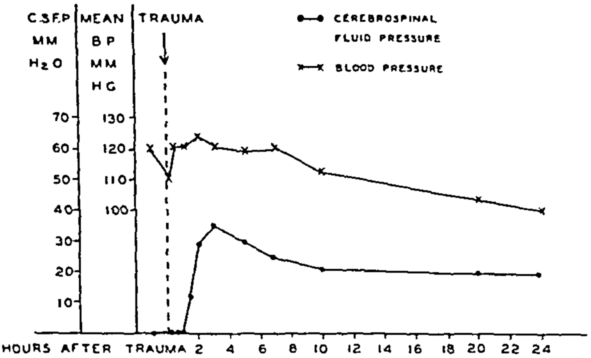

Chart 1 (dog T 56).—Effect of a 500 Gm. weight.

Group 3.—*Trauma by a 1,000 Gm. Weight; Animals Killed After Six Hours.*—The animals in group 2 exhibited an inconstant and not marked increase in intracranial pressure. The greatest change in the water content of their brains was found in those killed four or eight hours after trauma. Therefore, in the four dogs of group 3 the degree of trauma was doubled, and the animals were killed six hours after trauma. The results are shown in table 3.

The cerebrospinal fluid pressure was markedly elevated in three animals and moderately elevated in one, and these changes persisted without significant alteration until the termination of the experiments. The mean blood pressure showed some elevation in three of the four animals.

The average fluid contents of the various parts of the brain closely approximated or were slightly lower than the normal values in group 1, except in the cerebral gray matter, where the fluid content was slightly greater than the average normal in three of the four animals.

Group 4.—*Trauma by a 1,000 Gm. Weight; Animals Killed at the Time of the Maximum Increase in Cerebrospinal Fluid Pressure.*—Table 4 shows the results in this group of ten dogs. A marked increase in the cerebrospinal fluid

The fluid contents were again almost unexceptionally constant. The average values were not only slightly greater than the control levels but also exceeded slightly the average fluid contents observed in groups 4 and 5. In fact, the values in this group were higher than in any other group except group 2 C (table 7).

TABLE 5.—*Fluid Content of the Brains of Dogs Killed Immediately After Receiving 50 Cc. of 50 per Cent Solution of Dextrose Intravenously; Previous Trauma by a 1,000 Gm. Weight*

Dog No.	Interval Between Trauma and Injection of Dextrose, Hr.	Immediate Rise in Mean Blood Pressure, Mm. of Hg	Later Rise in Mean Blood Pressure, Mm. of Hg	Cerebrospinal Fluid Pressure		Fluid in Cerebral Gray Matter, %	Fluid in Cerebral White Matter, %	Fluid in Cerebellar Gray Matter, %	Fluid in Medulla Oblongata, %
				Maximum Increase Before Injection, Mm. of H_2O	Increase at Time of Killing, Mm. of H_2O				
T27	3½	20	9	140	±	80.2	69.5	79.6	73.8
T28	3	22	10	130	±	79.6	70.2	79.4	70.8
T29	7½	24	0	80	±	80.0	69.5	81.0	72.3
T30	4	69	0	200	±	80.8	68.9	79.7	72.3
T33	3½	13	0	110	±	79.2	66.6	78.2	80.0
Average						79.9	68.9	79.6	71.8

TABLE 6.—*Fluid Content of the Brains of Dogs Killed Two Hours After Receiving 50 Cc. of 50 per Cent Solution of Dextrose Intravenously; Previous Trauma by a 1,000 Gm. Weight*

Dog No.	Interval Between Trauma and Injection of Dextrose, Hr.	Immediate Rise in Mean Blood Pressure, Mm. of Hg	Later Rise in Mean Blood Pressure, Mm. of Hg	Cerebrospinal Fluid Pressure		Fluid in Cerebral Gray Matter, %	Fluid in Cerebral White Matter, %	Fluid in Cerebellar Gray Matter, %	Fluid in Medulla Oblongata, %
				Maximum Increase Before Injection, Mm. of H_2O	Increase at Time of Killing, Mm. of H_2O				
T32	7¾	27	0	65	10	81.2	70.4	80.3	72.0
T34	4	0	0	70	50	80.4	69.4	80.4	71.2
T35	3½	3	6	140	80	79.8	68.4	80.5	73.6
T36	5	8	0	40	65	81.0	68.0	80.6	71.7
T37	3	15	0	104	±	79.7	69.1	80.1	70.5
Average						80.4	69.1	80.4	71.8

GROUP 7.—*Lumbar Cerebrospinal Fluid Outflow in Untraumatized Dogs.*—In two dogs the outflow of cerebrospinal fluid from an 18 gage needle (the same needle was used in both experiments and in all experiments in group 8), measured in drops per minute, was determined over a period of twenty-four hours. The needle was inserted into the lumbar subarachnoid space with the animal's head in the holder, as in the preceding experiments, but with the body twisted to lie on its side. The needle was left open at all times.

During the first hour after lumbar puncture the outflow varied greatly from minute to minute, usually with a marked respiratory fluctuation. After this period of initial variation, the flow gradually assumed a relatively constant rate of one drop in one and one half to two minutes, and this rate was maintained throughout the twenty-four hours of observation.

Group 8.—*Effect of Trauma by a 1,000 Gm. Weight on the Lumbar Outflow of Cerebrospinal Fluid.*—The outflow was determined as in group 7, and the same initial fluctuation was observed in all of the six animals. However, a much slower control rate of flow was observed in three of the animals than in the two dogs of group 7. Trauma was administered two hours after lumbar puncture, when the outflow had assumed a constant rate.

The results observed were not consistent or conclusive (table 8). A variable and unsustained increase in flow usually occurred immediately after trauma. At later periods the rate of flow was relatively unchanged in three animals (T 39, T 40 and T 46), seemed to be definitely slowed in one (T 43) and showed some degree of sustained increase in two (T 42 and T 47).

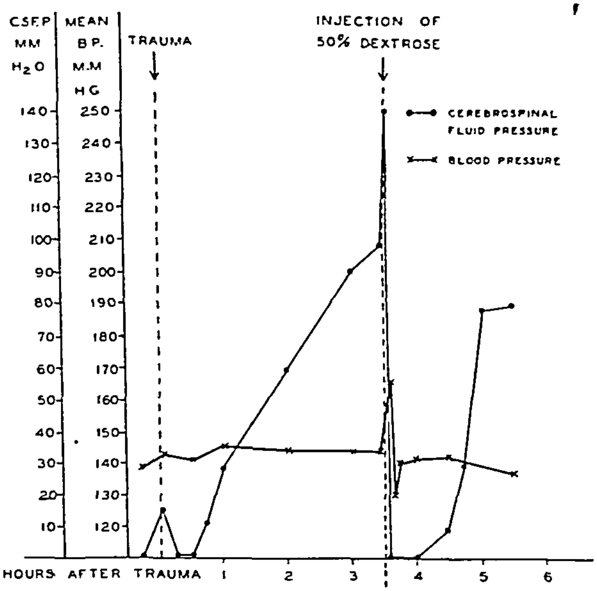

Chart 3 (dog T 35).—Effect of a 1,000 Gm. weight. Fifty cubic centimeters of 50 per cent solution of dextrose was injected three and one-half hours after trauma.

Group 9.—*Effect on Cerebrospinal Fluid Pressure of the Intracisternal Injection of Small Quantities of Physiologic Solution of Sodium Chloride.*—Before evaluating the significance of the small changes observed in the fluid content of the brain, it seemed essential to determine whether such small increases in the fluid content could be responsible for the rise observed in the cerebrospinal fluid pressure. Three dogs were used for this purpose. A three way stopcock was interpolated between the cisternal needle and the manometer, in order that fluid might be withdrawn or injected with only a momentary break in the pressure measurements.

After a normal constant cerebrospinal fluid pressure had been observed for one hour, a volume of physiologic solution of sodium chloride estimated to be equivalent to 0.5 per cent of the weight of the dog's brain was injected into the cisterna magna, and the stopcock was immediately turned back to reestablish communication between the cistern and the manometer. After the cerebrospinal fluid pressure was observed, the stopcock was opened to allow the escape of fluid until the pressure had been reduced to the normal level. The entire procedure was then repeated. In this way, several readings were obtained on each animal. Subsequently, twice the volume of saline solution originally employed was injected and pressure readings made as before, and finally the volume was again doubled to obtain another series of readings. These approximate volumes were employed because most of the average increases observed in the fluid content of the brain after trauma did not exceed 1 per cent. After the readings were completed, the brain was removed, free fluid blotted away and the brain weighed.

TABLE 7.—*Average Fluid Contents of the Brains in the Various Groups of Experiments*

Type of Experiment	Number of Experiments	Fluid in Cerebral Gray Matter, %	Fluid in Cerebral White Matter, %	Fluid in Cerebellar Gray Matter, %	Fluid in Medulla Oblongata, %
1. Normal controls	5	79.4	68.0	79.6	70.9
2a. Brain removed 2 hours after trauma by 500 Gm. weight	5	80.1	68.6	80.6	70.9
2b. Brain removed 4 hours after trauma by 500 Gm. weight	2	80.2	68.5	80.6	70.7
2c. Brain removed 8 hours after trauma by 500 Gm. weight	2	80.4	70.5	81.0	71.0
2d. Brain removed 24 hours after trauma by 500 Gm. weight	3	79.7	69.6	80.4	70.4
2. Average of 2a, 2b, 2c and 2d	11	80.1	69.1	80.6	70.8
3. Brain removed 6 hours after trauma by 1,000 Gm. weight	4	80.3	67.8	79.9	68.9
4. Brain removed at time of maximum cerebrospinal fluid pressure after trauma by 1,000 Gm. weight	10	80.0	68.9	79.8	70.4
5. Brain removed immediately after posttraumatic treatment with 50 per cent solution of dextrose	5	79.9	68.9	79.6	71.8
6. Brain removed 2 hours after posttraumatic treatment with 50 per cent solution of dextrose	5	80.4	69.1	80.4	71.8

TABLE 8.—*Outflow of Cerebrospinal Fluid Through a Lumbar Puncture Needle After Trauma by a 1,000 Gm. Weight*

Dog No.	Initial Rate, Drops per Minute	Immediately After Trauma, Drops per Minute	1 Hour After Trauma, Drops per Minute	2 Hours After Trauma, Drops per Minute	4 Hours After Trauma, Drops per Minute	24 Hours After Trauma, Drops per Minute
T39	1	3	1	1	1	3/4
T40	1/2	2	1	1/2	1/2	1/3
T42	1/6	11	1/3	1/2	1	—
T43	1/7	3/4	1/5	1/5	1/25	0
T46	1/2	2	1/2	1/3	0	—
T47	1/5	1/5	1/3	1/2	3/4	0

The results are shown in table 9. Only immediate pressure readings are included, since it was the purpose of these experiments to determine only the effects of the actual increases in the volume of the intracranial contents brought about by the injections. After injection of an amount of fluid equivalent to approximately 0.5 per cent of the weight of the brain, a definite but relatively slight rise in the cerebrospinal fluid pressure was observed, the greatest increase being 15 mm.

When a volume equivalent to approximately 1 per cent of the weight of the brain was injected, a greater increase in pressure was observed, the greatest being 60 mm. and the average 31 mm. This degree of rise in pressure is comparable to that found in some of the animals subjected to mild trauma (table 2) but does not approach that usually observed after more severe trauma (tables 3, 4, 5 and 6).

TABLE 9.—*Effect on Cerebrospinal Fluid Pressure of the Intracisternal Injection of Small Volumes of Physiologic Solution of Sodium Chloride*

Dog No.	Body Weight, Kg.	Weight of Brain, Gm.	Volume of Saline Solution Injected, Cc.	Percentage of Weight of Brain of Saline Solution Injected	Immediate Increase in Cerebrospinal Fluid Pressure, Mm. of H_2O	Increase in Cerebrospinal Fluid Pressure After 15 Sec.
T58	11.47	76	0.35	0.46	20	15
			0.35	0.46	15	10
			0.70	0.92	60	50
			0.70	0.92	55	40
			1.40	1.84	390	260
			1.40	1.84	450	280
T59	12.0	73	0.35	0.48	10	5
			0.35	0.48	5	±
			0.70	0.96	20	15
			0.70	0.96	10	5
			0.70	0.96	10	±
			1.40	1.92	120	100
			1.40	1.92	160	140
			0.70	0.96	15	10
T60	10.4	62	0.3	0.48	5	±
			0.3	0.48	10	5
			0.6	0.97	25	15
			0.6	0.97	40	25
			0.6	0.97	30	20
			1.2	1.94	205	150
			1.2	1.94	165	120

Injection of amounts of fluid equivalent to approximately 2 per cent of the weight of the brain produced an immediate marked increase in the cerebrospinal fluid pressure. This degree of increase was greater than that usually observed after severe trauma.

COMMENT

Before arriving at conclusions from the experiments reported herein, it is necessary to consider the several essential limitations inherent in the method of study.

It is impossible to determine the fluid content of the brain both before and after trauma in the same animal. Therefore, the only available basis for comparison consists of average findings in normal animals. This objection is obviated to some extent by the small degree of variation observed in the normal animals.

Similarly, in the experimental animals, in spite of occasional individual variations, the great majority of the individual findings did not vary significantly from the average of their groups.

After careful study of the tables, it seems justifiable to conclude that any change in average findings as great as 1 per cent of fluid content may be considered as beyond the probable limits of error of the method.

If the validity of the results is accepted within these limits, it is next in importance to recognize what degree of increase in the total intracranial contents is necessary to produce a significant increase in the cerebrospinal fluid pressure. The results of the experiments on the animals in group 9 (table 9) indicate a marked increase in the degree of rise in pressure resulting from increasing the intracranial contents more than the equivalent of 1 per cent of the weight of the brain. In other words, 1 per cent of the weight of the brain may be considered as the limit beyond which the quantity of intracranial contents cannot be increased without producing a marked rise in pressure. It is apparent that an increase in the tissue fluid comparable to that found in edematous tissues elsewhere in the body (from 2 to 6 per cent in tissue as dense as muscle[24]) could exist in the brain only if the remaining intracranial contents (i. e., blood and cerebrospinal fluid) were greatly diminished.

The rise in cerebrospinal fluid pressure observed in these experiments could conceivably arise from an increase in tissue fluids, in cerebrospinal fluid or in intracranial blood volume or from any combinations of alterations in their respective volumes which resulted in an increase in the total intracranial fluid volume.

A survey of the composite average results shown in table 7 shows at once that no great change in tissue fluids has resulted from trauma to the head in these experiments. In only two groups (2 and 6) were as many as two of the four types of brain tissue examined found to have as much as 1 per cent greater fluid content than was found in the average normal animal. On account of the striking uniformity of the results, it may be justifiable to conclude that a small increase in fluid content (particularly of the gray matter) probably follows trauma to the head. But the degree of increase observed was not in proportion to and probably should not be considered as the sole cause of the increase in cerebrospinal fluid pressure which occurred.

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[24] Pilcher, C.; Calhoun, J. A.; Cullen, G. E., and Harrison, T. R.: Studies in Congestive Heart Failure: V. The Potassium Content of Skeletal Muscle Obtained by Biopsy, J. Clin. Investigation 9:191, 1930. Harrison, T. R.; Pilcher, C., and Ewing, G.: Studies in Congestive Heart Failure: IV. The Potassium Content of Skeletal and Cardiac Muscle, ibid. 8:325, 1930.

The results of the experiments on the cerebrospinal fluid outflow, as stated previously, were not consistent or conclusive (table 8). From them it may be said only that the outflow of cerebrospinal fluid is increased in volume in some cases after trauma to the head, but this may not necessarily be an index of the production of cerebrospinal fluid, since the outflow would probably be increased by any alteration in intracranial contents producing increased pressure. Of interest in this connection are the findings of Hoff,[20] who injected fluorescein intravenously in estimating the production of cerebrospinal fluid and found an increase after measured trauma to the head. Recent experiments by Parker and Lehman [25] have demonstrated that a rise in the cerebrospinal fluid pressure occurs after replacement of small amounts of cerebrospinal fluid with equal volumes of blood serum, defibrinated blood or solution of hemoglobin but not after replacement with washed red blood cells. The authors concluded: "It is probable that the phenomena reported are the result of the increase of osmotic pressure of the cerebrospinal fluid due to the introduction of blood proteins."

The results of experiments on the effect of hypertonic solution of dextrose (table 5 and 6) confirm, for the first time in traumatized animals, the original observations of Weed and McKibben,[26] Weed and Hughson [27] and many later investigators on the reduction of cerebrospinal fluid pressure after the intravenous administration of these solutions. Further, they are not incompatible with the alterations in the bulk of the brain found by Weed and McKibben [28] after intravenous injections of solutions of various concentrations, for these alterations may well have been due to changes in such factors as ventricular size or intracerebral blood volume.

The results of the experiments reported herein also confirm the findings of Masserman,[29] who measured the cerebrospinal fluid pressure in untraumatized human subjects receiving intravenous injections of hypertonic solutions. He observed an original fall in pressure followed by a rise to a level equal to or greater than the control value. The present experiments suggest that in traumatized dogs concomitant with this secondary rise in pressure, there may be an increase in the cerebral tissue fluid greater than that present before the injection. These findings cast considerable doubt on the wisdom of the intravenous use of hypertonic solutions in the treatment of injuries of the head.

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[25] Parker, W. P., and Lehman, E. P.: Personal communication to the author.

[26] Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebro-Spinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **48**:512, 1919.

[27] Weed, L. H., and Hughson, W.: Systemic Effects of the Intravenous Injection of Solutions of Various Concentrations, with Especial Reference to the Cerebrospinal Fluid, Am. J. Physiol. **58**:53, 1921.

[28] Weed, L. H., and McKibben, P. S.: Experimental Alteration of Brain Bulk, Am. J. Physiol. **48**:531, 1919.

[29] Masserman, J. H.: Effects of Intravenous Administration of Hypertonic Solutions of Dextrose, with Special Reference to the Cerebrospinal Fluid Pressure, J. A. M. A. **102**:2084 (June 23) 1934.

Regarding intracranial blood volume, there is little evidence. Wolff and Blumgart[30] found a decrease in the velocity of blood flow through the brain after increasing the cerebrospinal fluid pressure through a needle in the cisterna magna. However, they believed that "through cerebral vasodilatation, the flow, though slowed, is increased in volume . . ." Pilcher,[31] using the arteriovenous oxygen difference method, found a decrease in the volume flow of blood through the brain after the intravenous injection of hypertonic solutions in normal dogs. The only observations on the actual intracerebral blood volume are those of Weil, Zeiss and Cleveland,[32] who injected colloidal silver intravenously and determined the silver content of the brain (which does not remove colloidal silver from the blood). They found an increase in the blood volume of the brain immediately (from five to fifteen minutes) after the intravenous injection of 15 per cent sodium chloride. There are no recorded observations pertaining to intracranial blood volume after cerebral trauma. It seems probable that this may be an important factor in the mechanism producing the increased cerebrospinal fluid pressure which follows trauma to the head.

SUMMARY AND CONCLUSIONS

The fluid content of various portions of the dog's brain has been determined after measured trauma of varying degrees.

After trauma sufficient to produce a definite elevation in the cerebrospinal fluid pressure, the fluid content of the brain was slightly, if at all, increased above the average normal level. The small average increase observed is not believed to be sufficiently great to account for the elevation of the cerebrospinal fluid pressure.

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[30] Wolff, H. G., and Blumgart, H. L.: The Cerebral Circulation: VI. The Effect of Normal and Increased Intracranial Cerebrospinal Fluid Pressure on the Velocity of Intracranial Blood Flow, Arch. Neurol. & Psychiat. **21**:795 (April) 1929.

[31] Pilcher, C.: Cerebral Blood Flow: I. The Effect of Intravenous Administration of Hypertonic and Hypotonic Solutions on the Volume Flow of Blood Through the Brain, Arch. Neurol. & Psychiat. **24**:899 (Nov.) 1930.

[32] Weil, A.; Zeiss, F. R., and Cleveland, D. A.: The Determination of the Amount of Blood in the Central Nervous System After Injection of Hypertonic Solutions, Am. J. Physiol. **98**:363, 1931.

There is no conclusive evidence in these studies, or in those of other authors, indicating the existence of marked posttraumatic cerebral edema.

The outflow of lumbar cerebrospinal fluid after trauma to the head was not consistently altered but in some instances showed a sustained increase.

It seems probable that other factors, such as cerebrospinal fluid volume and intracranial blood volume, are of greater importance than cerebral edema in producing the increased intracranial pressure which follows trauma to the head.

DISLOCATION AND FRACTURE-DISLOCATION OF LOWER CERVICAL VERTEBRAE

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Nearly as far back as one is able to peruse the annals of medical history one finds references to fractures and fracture-dislocations of the cervical portion of the spine. An injury involving this segment of the spine rightly struck terror into the heart of the surgeon who was called on to treat it. About 2500 B. C. the timidity of a surgeon regarding such an injury was recorded in a papyrus written during that period, in which it was stated:[1] "One having a crushed vertebra in his neck, he is unconscious of his two arms and his two legs, and he is speechless. An ailment not to be treated." The reluctance to treat such a lesion can only be surmised.

Hippocrates[2] formed a rational and sound plan for the treatment of a lesion of this type in the acute stage. His method consisted in extension of the head with the patient in a recumbent position. Despite his teachings his contemporaries were prone to practice a form of therapy called succussion. The unfortunate patient was placed on a vertical ladder with the head down. The ladder was then shaken forcefully in the hope that reposition of the involved vertebra might take place. Needless to say, the torture experienced by the patient was terrific, and the mortality rate was high. The father of medicine decried such a brutal manner of treatment but his laments were of no avail at that time. It is to him, however, that the modern nonoperative form of treatment for such a lesion owes its origin, although various physicians have introduced minor modifications of his principle.

Guy de Chauliac[3] and others who dominated the surgical world about the fifth century used much the same method of treatment as

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[1] Breasted, James H.: The Edwin Smith Surgical Papyrus, Chicago, University of Chicago Press, 1930.

[2] The Genuine Works of Hippocrates, translated by Francis Adams, New York, William Wood & Company, 1929.

[3] de Chauliac, Guy: On Wounds and Fractures, translated by W. A. Brennan, Chicago, W. A. Brennan, 1923.

Hippocrates. Paré,[4] who contributed greatly to the knowledge of traumatic lesions, obtained many good results by traction exerted on the extended head.

Skepticism as to the wisdom of attempting reduction of a fracture of a cervical vertebra was universal during the early part of the nineteenth century. Boyer[5] said: "Any attempt at setting these fractures would not only be useless but dangerous, by the straining it would occasion." Cupping and scarification of the cervical region, as well as the use of setons and ointments, were recommended by him, and these appear to have been the only armamentarium resorted to by the surgeons of his day.

Chelius[6] admitted that the patient with such a fracture might be left alone. He said that the pain would gradually subside and that the patient would have no inconvenience other than an unnatural position of the head and restricted motion. Fearful lest the spinal cord be torn asunder by manipulation or matters be made worse, Dupuytren,[7] and others agreed to this policy of laissez faire. The attitude of the medical profession in regard to lesions of this nature can be summed up in the words of Abernethy:[8] "They are cases so generally fatal, that I am convinced an assembly of old surgeons would doubt that there was a possibility of recovery in any case." One is thankful that these teachings as regards traumatic lesions of the cervical portion of the spine in the acute stages have been discarded.

In 1814 Henry Cline performed what is now known as laminectomy for the removal of pressing vertebral arches. His operation was designed primarily for the treatment of fracture of the spine, but at that time the operation was met with a storm of criticism. A strong controversy arose between Sir Astley Cooper[9] and Sir Charles Bell as to the value and propriety of resection of the vertebral arches. As a result of this operation, as well as of the controversy which arose. the medical profession was shaken from the doldrums of thought in regard to these lesions, and greater interest was stimulated.

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4. Paré, Ambroise: The Workes of that Famous Chirurgion Ambrose Parey, translated by T. Johnson, London, Mary Clark, 1678.

5. Boyer, Alexis: The Lectures of Boyer upon Diseases of the Bones, arranged by A. Richerand and translated by M. Farrell, London, John Callow, 1807.

6. von Chelius, M. J.: System of Surgery, translated by John F. South, London, Henry Renshaw, 1845.

7. Dupuytern, Guillaume: On the Injuries and Diseases of Bones, translated and edited by F. leGros Clark, London, Sydenham Society, 1847.

8. Abernethy, John: Lectures on Anatomy, Surgery and Pathology, London, James Bullock, 1828.

9. Cooper, Astley, P.: A Treatise on Dislocations and on Fractures of the Joints, ed. 2, London, Longman, Hurst, Rees, Orme and Browne, 1823.

Ashhurst[10] in 1867 reviewed the literature on the subject. The treatise which he wrote is an admirable one, constituting a profound advancement in the knowledge of this type of lesion in regard to diagnosis and the pathologic picture. Concerning paralysis, he said:

> The cause of paralysis in some cases is obscure. In fatal cases the postmortem appearances have consisted in effusion of blood with softening of the cord structure, but in some cases which have recovered, the paralysis has been so ephemeral as to give rise to the impression that the cause has been congestion rather than actual extravasation.

In regard to diagnosis, he stated:

> If paralysis below the seat of injury be immediate, complete and permanent, there is every reason to fear that the cord has been absolutely divided. If paralysis is immediate but not permanent it is probably a case of contusion of the cord without structural damage. If paralysis comes on as a late sign, increases to a certain point, then to diminish again, it is probably an effusion, within or without the cord which, under favorable circumstances, may be absorbed. If paralysis is progressive, if not arrested, it will invariably sooner or later prove fatal.

From the literature Ashhurst collected reports of 212 cases of injury to the cervical region of the spine. The mortality rate in this series was 77 per cent; 18 per cent of the patients recovered from the injury and 3 per cent were relieved. The treatment was by extension, resection or simple general care of the patient.

In 1869 Blasius[11] collected reports of 159 cases of definitely diagnosed dislocation of the cervical portion of the spine. In 123 of these cases the injury proved fatal, while in 36 there was improvement. In the cases of bilateral forward dislocation, the severest type, there was a mortality rate of 92.6 per cent.

These startling statistics alarmed and aroused surgeons who saw the inadequacy of the treatment for this type of lesion. A method of reduction was described by Walton[12] in 1889. This method is still in use at the present time and is called the retrolateral flexion maneuver with rotation. Walton reported 5 cases of dislocation of the cervical vertebrae in which he used this treatment. A few years later Wagner and Stolper[13] described a method of reduction which, in the main, is similar to that of Walton.

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[10] Ashhurst, John, Jr.: Injuries of the Spine, Phliadelphia, J. B. Lippincott & Co., 1867.

[11] Blasius, E.: Die traumatischen Wirbelverrenkungen, Vrtljschr. f. d. prakt. Heilk. **102**:1, 1869; **103**:46, 1869; **104**:77, 1869.

[12] Walton, George L.: Dislocation of the Cervical Vertebrae, Boston M. & S. J. **120**:277, 1889.

[13] Wagner, W., and Stolper, P.: Die Verletzungen der Wirbelsäule und des Rückenmarks, in Billroth, T., and Luecke, G. A.: Deutsche Chirurgie, Stuttgart, F. Enke, 1898, no. 40, p. 385.

With the advent of the roentgen rays, one became able to evaluate each lesion. This led to a safer and saner manner of treatment and improved results.

Taylor[14] in 1929 described a method of reduction by means of forceful traction exerted on the extended head. Nine persons were treated by him. After reduction had taken place, the head and neck were immobilized in a plaster helmet. He stated that immobilization was imperative until bony ankylosis had taken place between the vertebral bodies and that bony ankylosis always took place.

One year later Langworthy[15] reported 30 cases of dislocation of the cervical vertebra in which treatment was given by him. Reduction was obtained by traction in cases of unilateral as well as of bilateral injury. The mortality rate in this series was 30 per cent. Diagnosis of a unilateral dislocation was made from physical examination and by the fact that the patient was cured by manipulation of the head.

The literature on fracture-dislocation of the cervical portion of the spine is voluminous; yet nearly all of the articles concern the lesion in the acute stage. Many persons with injury to the cervical portion of the spine survive the acute stage but have residual symptoms. Reports of series of cases which have been cited deal mostly with the condition in the acute stage.

Only a limited number of articles could be found which dealt with the residual effects of the more acute lesions and their treatment. De Quervain and Hoessly[16] in 1917 transplanted the spine of the scapula between adjacent cervical vertebrae to produce a fusion of these in an attempt to relieve 2 patients suffering from the residual symptoms caused by an earlier fracture-dislocation. As far as the function of the neck and the relief of preoperative symptoms were concerned, the results were reported as excellent. Hibbs[17] in 1922 reported a case of fracture-dislocation of the cervical portion of the spine in which fusion was employed to relieve the patient from symptoms arising from a previously treated injury of that portion of the spine. The patient was greatly benefited by this procedure. In 1930 Krida[18] reported a dislocation of the fifth cervical vertebra in a patient on whom repeated attempts at

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[14] Taylor, Alfred: Fracture Dislocations of the Cervical Spine, Ann Surg. **90**:321, 1929.

[15] Langworthy, M.: Dislocations of the Cervical Vertebrae, J. A. M. A. **94**: 86 (Jan. 11) 1930.

[16] de Quervain, F., and Hoessly, H.: Operative Immobilization of the Spine. Surg., Gynec. & Obst. **24**:428, 1917.

[17] Hibbs, Russell A.: Fracture-Dislocation of the Spine Treated by Fusion, Arch. Surg. **4**:598 (May) 1922.

[18] Krida, Arthur: Dislocation Between Fifth and Sixth Cervical Vertebrae: Delayed Operative Reduction and Fusion, Am. J. Surg. **9**:560, 1930.

closed reduction had been carried out, all of which were followed by redislocation. After these attempts a portion of the cervical segment of the spine was fused; the patient was relieved from symptoms as well as from the danger of redislocation.

Cases in which the patient presents the residual effects of trauma to the cervical region have been little discussed, and it is the purpose of this paper to evaluate spinal fusion and laminectomy in reference to treatment and prognosis in cases in this category.

PRESENTATION OF CASES

Between 1923 and 1933 18 patients with dislocation or fracture-dislocation of the lower cervical vertebrae were admitted to the New York Orthopaedic Dispensary and Hospital. The average age of these patients was 29, the youngest being 19 and the oldest 55. Fourteen of the patients were men, and 4 were women. With the exception of 2 patients, the original trauma had taken place some time prior to the patient's first visit to this hospital. Two patients were seen two days after the accidents which were responsible for the lesions, while 1 was seen two weeks after the original trauma. The longest interval was sixteen years, and the average interval, sixteen months. Although there are 2 patients in the series who could be designated as having fracture-dislocation of the more acute type, the entire series is regarded as presenting the residual manifestations of acute traumatism of the lower cervical segment of the spine.

TABLE 1.—*Diagnosis and Type of Operation in Series of Cases**

Case	Diagnosis	Operation
1	Fr.-dis. 5 C	Spinal fusion 4 C-7 C; laminectomy 4 C and 5 C
2	Fr.-dis. 3 C	Spinal fusion 2 C-7 C
3	Fr. 6 C	Spinal fusion 5 C-7 C
4	Fr. 5 C	Spinal fusion 4 C-6 C
5	Fr.-dis. 5 C	Spinal fusion 4 C-6 C
6	Dis. 6 C	Spinal fusion 6 C-1 D
7	Fr.-dis. 6 C	Spinal fusion 5 C-1 D
8	Dis. 4 C	Spinal fusion 2 C-5 C
9	Fr.-dis. 5 C	Spinal fusion 4 C-6 C
10	Dis. 5 C	Spinal fusion 3 C-6 C; laminectomy 3 C-6 C
11	Fr.-dis. 4 C	Spinal fusion 3 C-6 C; laminectomy 4 C-5 C
12	Fr.-dis. 5 C	Spinal fusion 5 C-7 C
13	Fr. dis. 6 C	Spinal fusion 5 C-7 C
14	Dis. 4 C	Spinal fusion 4 C-5 C; laminectomy 4 C
15	Dis. 5 C	Spinal fusion 4 C-6 C
16	Dis. 5 C	Spinal fusion 5 C-7 C
17	Fr.-dis. 6 C	Spinal fusion 5 C-7 C; laminectomy 5 C
18	Fr.-dis. 4 C	1. Spinal fusion 3 C-6 C 2. Laminectomy 4 C-5 C 3. Laminectomy 3 C-6 C; partial excision of verterbral body 5 C

* The abbreviations may be interpreted as follows: Fr.-dis. 5 C, fracture-dislocation of the fifth cervical vertebra, etc.

The diagnosis and type of operation performed in each case are recorded in table 1.

CAUSE OF FRACTURES AND FRACTURE-DISLOCATIONS OF THE CERVICAL PORTION OF THE SPINE

The cervical portion of the spine has a wide range of mobility, which is dependent on many factors. The ligaments are long enough to allow great mobility, and they do not check flexion before the anterior lips of the bodies are about in contact. The ligamentum nuchae, which in the pronograde mammals acts as a powerful check to flexion, is almost useless for this purpose in man because it is not so fully developed. The articular capsules of the lateral articulations are thin and redundant in the cervical portion of the spine. The capsules, by their inability to constrain the articulations from excessive motion, permit them to glide forward into a luxated state. The cervical bodies are small, separated from each other by a relatively greater amount of intervertebral substance than is found in other areas of the spine. Likewise the lateral articulations are on a more horizontal plane, not only facilitating the motion of flexion but increasing the ease of dislocation.

Mechanically the cervicodorsal junction is unstable. It is a point where the rather flexible cervical portion of the spine meets the comparatively immobile dorsal segment. Naturally, a force exerted on the flexible segment, if of sufficient strength, will cause damage to it rather than to the relatively immobile portion. Forces tend to be concentrated on the areas where fixed and movable portions of the spine meet, as at the cervicodorsal junction.

The cervical segment of the spine, being deficient in so many stabilizing factors, having a mechanical situation which renders it vulnerable and yet being called on to furnish great ranges of mobility, gains its stability at the expense of voluntary and involuntary muscular effort. By involuntary muscular effort is meant the neuromuscular mechanism which maintains the head and neck in an erect posture during the conscious state. The muscles surrounding the cervical portion of the spine are many, and collectively they are very strong. Acting under voluntary control against a given force, these muscles are capable of protecting the spine in most instances. There are times, however, when this muscular control is off guard or is not of sufficient strength, and it is during these unguarded moments that injury to the cervical segment of the spine takes place. The degree of injury which may ensue depends on the extent of the force applied, as well as on the duration of the unguarded moment.

In this series of cases it was almost uniformly found that injury to the cervical portion of the spine had been received during a moment when the spine was not protected by a sufficient amount of muscular effort, as well as when a force producing acute flexion was applied. Seven of the 18 patients gave a history of having struck the bottom of a swimming pool while diving. As the occiput struck the unyielding bottom the oncoming weight of the trunk and legs forced the head into acute flexion. Two patients were playing football and, while in a sitting position, were struck on the back of the head by another player, thus forcing the head into acute flexion. Injuries had been received in 2 instances when patients had fallen down stairs, bending the head forward during the fall. One case was unusual in that the injury had been received when the patient fell from the height of a few feet, landing on the buttocks. Perhaps in this case injury to the cervical portion of the spine had been caused by the snapping forward of the head, an accident which sometimes occurs in such a fall. The exact manner of the injury was not stated by a few patients.

The series, although small, emphasizes that the mechanism which causes fractures and dislocations in this area of the spine is flexion.

ORIGINAL TREATMENT

The original treatment in 3 of the 18 cases was rest in bed for a few weeks. Reduction of the lesion was attempted in 4 instances by the use of traction on the head. In 1 case traction on the head was followed by the application of a head helmet. This helmet was worn for a few weeks after its application. Manipulation of the head, followed by no supportive apparatus, was the original treatment in 3 cases. In 2 cases osteopathic or chiropractic manipulations were resorted to by the patients. Three patients were not seen elsewhere before they came to this hospital, while 2 did not present any history as regards original treatment.

PREOPERATIVE STATUS OF PATIENTS

Disability was the reason for each of the patients in this series applying to the hospital for treatment. Disability from this type of lesion, whether it is in an acute or a chronic stage, is dependent chiefly on the type and extent of injury to the cord, but partly on the degree of involvement of nerve roots and partly on the extent and type of structural damage to the vertebral column with its supportive structures.

Injury to the cord at the time of primary trauma can occur as the result of concussion, contusion, edema, hematomyelia or laceration. The degree of damage to the cord with its resultant syndromes depends on the type, extent and location of any one or a combination of these. After the integrity of the cord has been affected in any of the foregoing manners, its function may return gradually and, in the milder lesions, will sometimes return to normal, the patient suffering no disability because of the lesion of the cord. As a result of irreparable damage to the cord at the primary trauma, the disability of the patient may be of any degree and of a lasting nature. despite perfect anatomic reduction. Some of the factors which may operate in causing continued damage to the cord are abnormally luxated vertebrae, pressing vertebral arches and bodies and sclerosis of the coverings of the cord.

To diagnose the presence of involvement of the cord is usually easy. This was true in most of these cases, yet it was difficult to form a satisfactory opinion as to the nature of the pathologic process causing the dysfunction. In the presence of dysfunction of the cord it is sometimes difficult to ascertain whether the dysfunction is due to the original trauma or to latent factors.

The neurologic syndromes, indicating the evidence of involvement of the cord in these cases, will not be presented in detail, but it may be stated that 3 patients with severe syndromes were bedridden when they were first seen at this hospital. An atypical Brown-Séquard phenomenon was present in 1 of these, the lesion being at the level of the fifth cervical segment. Milder and moderate syndromes included atrophy, hemiplegia and contracture as well as other evidence of damage to the cord.

A fracture-dislocation in the cervical portion of the spine, perfectly reduced, may still produce disability in the function of the neck. Such disability may be caused by mobility at fractures of the posterior elements, arthritic productions arising from traumatized lateral articulations, scar formation from the tearing of ligaments or articular capsules and unstable vertebrae.

If unreduced, a malalined cervical segment of the spine may also produce symptoms referable to the head and neck. These symptoms may occur as a result of the aforementioned causes, as well as from impingement of the spinous processes and laminae.

Eight patients in the series had partial rigidity of the neck associated with severe pain in the cervical region. In another instance there was severe pain in this region without any limitation of the motion of the head. Limited motion and an unnatural position of the head were complained of by 1 patient. Stiff neck, limited motion of the head of a mild degree, a grating sensation of the cervical region and a moderate ache in the posterior cervical region were complained of by many patients. All of these symptoms were indicative of a pathologic process of the ligamentous and bony structure of the spine.

Many patients in the series complained of symptoms which would indicate involvement of the nerve roots. In cases of injury in which the cervical segments of the cord were damaged it was difficult in some instances to ascertain whether there was sufficient evidence to warrant the diagnosis of the presence of a pathologic process involving the nerve roots. The radicular type of pain, various atrophies, contractures or sensory disturbances involving the upper extremity would lead one to suspect trauma to the cervical nerve roots in many patients. Some of the patients presented no evidence of involvement of the cord, and yet there were neurologic syndromes present which, without doubt, could be explained only by the presence of a radicular lesion.

Patients with evidence of involvement of the nerve roots suffered neuralgic pains down the arms and weakness and atrophy of the various muscle groups of the scapula and humerus and of the arm, forearm and hand. Hypesthesias and paresthesias were also frequently present.

A syndrome referable to the head and neck, which was caused by either a bony or a ligamentous pathologic process, has been designated as a vertebral syndrome. The degree of the syndromes arising from involvement of the vertebral column, the nerve root and the spinal cord is given in table 2. In practically all of the cases there was a combination of one or more of these syndromes in the preoperative status of each case.

TABLE 2.—*Preoperative Status of Patients*

Case	Vertebral Syndrome	Nerve Root Syndrome	Cord Syndrome
1	None	Moderate	Severe
2	Moderate	None	None
3	Mild	Moderate	None
4	Mild	Mild	Moderate
5	Mild	Moderate	None
6	Moderate	None	None
7	Mild	Moderate	Mild
8	Moderate	Mild	None
9	Moderate	Mild	None
10	Moderate	Mild	None
11	Moderate	Mild	Severe
12	Moderate	None	Mild
13	Moderate	None	None
14	Mild	Moderate	None
15	Moderate	Mild	None
16	Mild	Moderate	None
17	Mild	Mild	Severe
18	Moderate	Moderate	Mild

PREOPERATIVE ROENTGENOGRAMS

Since there were only 10 cases in which preoperative and postoperative roentgenograms were available, only these will be referred to in connection with roentgenography. As a rule, anteroposterior and lateral views are taken of this type of lesion; however, stereoscopic and oblique roentgenograms are made in special instances. Special views are seldom necessary because these rarely give information in regard to the lesion which cannot be estimated from the routine views.

Anterior displacement was present in all of these cases, the amount of displacement of the luxated vertebrae varying from 5 to 80 per cent of the total horizontal diameter of the vertebral body. The amount of anterior vertebral tilt ranged from a minimum of 12 degrees to a maximum of 58 degrees, and tilt was present in all of the cases. Wedging constitutes a decrease in the vertical diameter of the involved vertebra anteriorly, while compression constitutes a decrease in the vertical diameter both anteriorly and posteriorly. In many of the cases there was a combination of these. In 5 cases there was no wedging, while in the remaining 5 cases this varied from 6 to 17 per cent of the anterior vertical diameter of the involved vertebra. Compression was not present in 6 cases, and in 4 it ranged from a few to 20 per cent. A lateral wedging of 7 per cent was a feature in 1 case, while in the remaining cases this deformity was not present. Bony ankylosis was not found in any of the 10 cases studied roentgenographically. This is of interest in that the patients were seen many months and sometimes years after their primary injury had occurred.

In case 2 (fig. 1) the body of the fifth cervical vertebra was fractured vertically, with the anterior fragment displaced anteriorly 15 per cent and the posterior fragment displaced posteriorly 30 per cent. In case 9 (fig. 2) there was a fracture-dislocation of the fifth cervical vertebra, but the spinous processes of the fourth and the fifth cervical vertebra were widely separated. Separation should have taken place between the spines of the fifth and sixth cervical vertebrae, unless a fracture of the posterior elements was present. The roentgenographic appearance was indicative of a fracture of the posterior elements, and in this instance operative findings confirmed the diagnosis. Arthritic deposits were a feature in 1 instance and could well account for the complaints referable to the vertebral column. An ununited fracture of the arch could be seen in only 1 case, while in another instance there was the appearance previously noted which suggested a fracture.

In all of the cases in the series diagnosis as to the nature of the lesion was made by roentgenographic examination.

TREATMENT

In 3 cases in which the patient was seen fairly recently after injury an attempt was made to reduce the lesion. This was done by means of 10 pounds of traction on the head exerted with the head in a slightly extended position. Complete reposition of the involved vertebra was not accomplished in any instance, yet relief from pain was experienced by the patient, and the muscular spasm was diminished. Forceful extension was not used to reduce the lesion in any instance. Preoperative care consisted mainly in the partial immobilization of the spine by sand-bags placed on either side of the patient's head, while pain was relieved by rest and the use of sedatives. The patients were operated on within a few days after entering the hospital.

In 13 cases fusion of the spine was carried out. A combined one stage laminectomy and spinal fusion were performed in 5 other instances. When spinal fusion alone was done, the average operating time was one hour and twenty-five minutes; the longest operating time was one

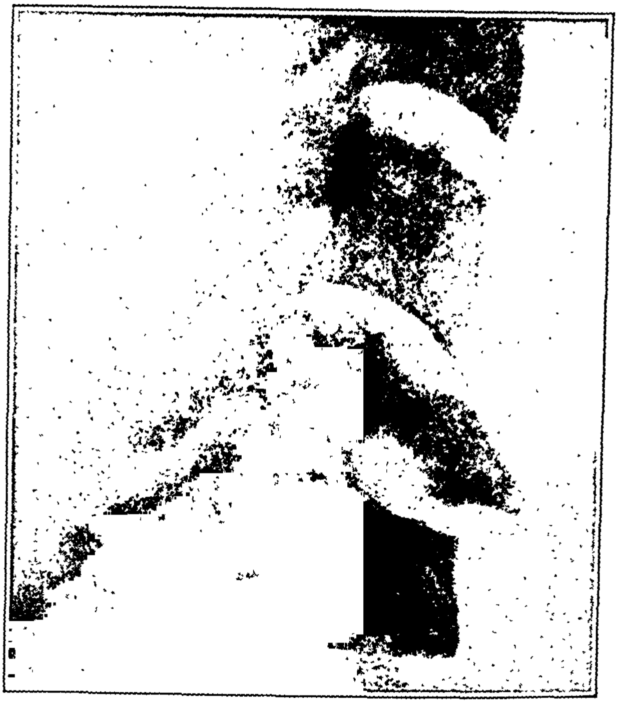

Fig. 1 (case 2).—Roentgenogram showing severe compression fracture of the body of the fifth cervical vertebra.

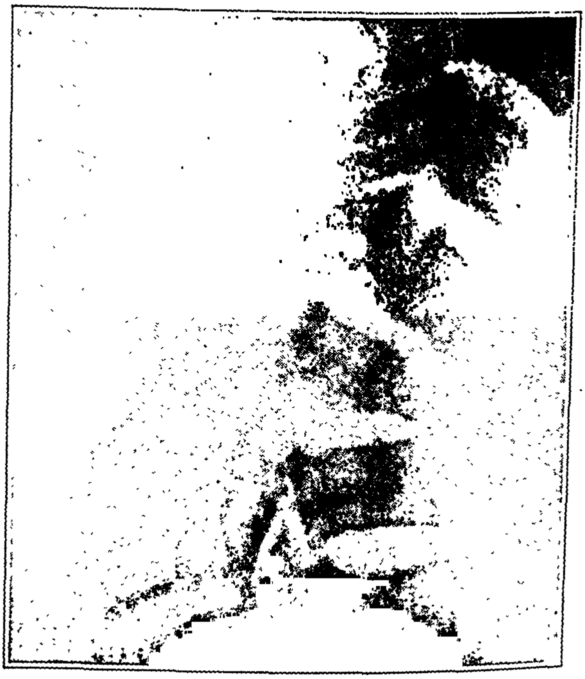

Fig. 2 (case 9).—Roentgenogram showing a fracture-dislocation of the fifth cervical vertebra.

hour and fifty minutes, while the shortest time was forty-five minutes. In those cases in which the combined procedures were done the average operating time was one hour and fifty minutes. Two hours and thirty-five minutes was the maximum operating time, while the minimum was one hour and twenty minutes.

In 1 instance the operator attempted to replace the dislocated articular facets without success. In another instance a freely movable fractured arch was encountered. This was removed lest the cord be damaged at a later date. In 1 case further surgical work was done. In only 1 case were the coverings of the cord opened intentionally at the primary operation.

Fig. 3 (case 18).—Preoperative roentgenogram showing the greatest degree of anterior vertebral tilt and the greatest percentage of anterior displacement of the involved vertebra observed in any case in the series.

The Hibbs type of spinal fusion was carried out in all instances. This operation consists in the subperiosteal exposure of the laminae, spinous processes and lateral articulations of the vertebrae to be fused. The ligamentum flavum and cartilage from the lateral articulations were removed. Lateral articulations and their processes were then comminuted. Interdigitating bone chips taken from the spinous processes and laminae were turned in such a manner as to bridge across the intervening interlaminar spaces. In the 5 cases in which laminectomy was performed, a bilateral type of laminectomy was done, followed by fusion of the portions of the laminae which were not removed, as well as of the lateral articular processes.

During the operation the patient was in a prone position on the operating table, with the head supported in a head rest. The head rest consisted of a tripod with a horizontal padded loop, which fitted the conformity of the face. With this type of head rest the anesthetist was not hampered in his work, the patient was in a comfortable position, and his head could be changed at any angle desired by the operator.

Because of the proximity of vital centers, surgical intervention in this area of the spine is dangerous unless caution is practiced by the operator. The cervical segment of the spine lies rather deep, so that an extensive exposure is necessary. Usually exposure of the spinous processes of two vertebrae above and two below the seat of injury is required, as this will insure a sufficient operative field with the minimum of retraction force. When spinal fusion or laminectomy of this area of the spine is performed, it should be borne in mind that the posterior elements are smaller than elsewhere and the interlaminar spaces are wider. Needless to say, curetting of ligaments, turning down of bone chips or removal of the laminae should be done with the utmost care.

Immediately after the operation the usual care was the application of a few pounds of traction on the head with the head immobilized by sand-bags. In a few instances sand-bags alone were used, but traction on the head not only aids in immobilization but tends to relieve muscular spasm. The head is placed in a slightly extended position by means of a small pillow beneath the patient's shoulders. In this manner the proper position of the head is maintained until fusion becomes firm.

Constant nursing of the patient is imperative until he is fully conscious, lest the head be moved during the interval when he is recovering from the anesthetic. Even during the first few days postoperatively the patient can be turned from one side to the other at frequent intervals, traction on the head and the sand-bags, of course, being removed before turning. In this manner nursing care of the patient is facilitated, and the patient is made more comfortable. After two weeks the patient can be placed on his side for longer periods.

OPERATIVE FINDINGS

Among the more frequent findings which were noted at operation was the formation of scar tissue, and in a few instances old extravasated blood was found in the soft tissues about the spine posteriorly. Impingement of spinous processes and laminae was noted in 5 cases. In 7 cases ununited fractures of the posterior elements were found. In most of these the fractured portion of the vertebral arch was freely movable. Hypermobile luxated vertebrae were encountered in 6 cases. Complete bilateral dislocation of the articular facets was noted in 4 cases, while a severely crushed articular process was found in another case. Natural fusion of impinging laminae was present in 1 case. Frequently the laminae of the vertebra involved were displaced anteriorly, and in 3 instances these laminae were removed because they encroached on the cord. In 1 instance moderate anterior displacement of a lamina had caused an indentation on the cord.

POSTOPERATIVE COURSE

Little evidence of shock or other complications were present in these cases, and the immediate postoperative reactions were, as a rule, of a mild degree. An exception to this statement was a patient in whom severe hemiplegia developed after spinal fusion, and further surgical treatment was later necessary. Slight edema of the occipital region and of the face was encountered postoperatively in 2 cases, and a generalized weakness of the extremities was present in 2. These complications lasted for only a few days, and no permanent damage was done to the cord. In a few cases there was a slight degree of abdominal distention, and in 2 cases urinary retention was present. These complications gave no alarm and were transient.

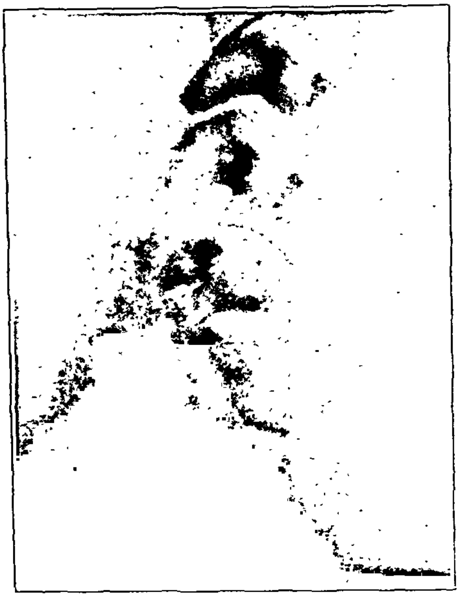

Fig. 4.—Postoperative roentgenogram showing solid bony fusion of the posterior elements while the involved vertebral body remains without bony ankylosis.

During their stay in the hospital all these patients, with the exception of those on whom further surgical measures were necessary, showed some degree of improvement in comparison with their preoperative status. The greatest and most constant improvement was in the amelioration of symptoms arising from the vertebral pathologic process. Symptoms arising from involvement of the nerve roots were slightly improved but with little change in comparison to the preoperative condition. One patient with severe involvement of the spinal cord was greatly improved, while 2 with severe involvement were only slightly improved. Control of the sphincter muscle, however, had returned, and the patients were able to get about with the aid of crutches, whereas before they entered the hospital they had been bedridden.

Fig. 5.—Postoperative roentgenogram showing solid bony fusion of the posterior elements and bony ankylosis of the involved vertebrae.

With the exception of the 1 patient who came to secondary operation two weeks following the primary operation, the remaining 17 were allowed out of bed, with no supportive apparatus, in from six to twelve weeks postoperatively. These patients were discharged from the hospital wards in from seven to thirteen weeks postoperatively. The remaining patient in the series was discharged one year postoperatively. During the stay in the hospital this patient was in bed continuously.

FOLLOW-UP STUDY

The longest postoperative follow-up period in this group was six years and the shortest two months, while the average period was two years. After discharge from the wards the patients were seen at fairly frequent intervals in the dispensary. Almost immediately after discharge physical therapy in the form of massage of the cervical region, along with active and passive motion of the cervical portion of the spine, was started. Muscle training and reeducation of partially paralyzed groups of muscles were also carried out for a long period, while various mild contractures were dealt with by the aforementioned types of therapy as well as stretchings.

After spinal fusion of the cervical region in which two or more vertebrae are fused, one would naturally suppose that the mobility of the head would be limited to a considerable degree. However, this was not the case in this series, for 13 of the 18 patients presented free, unrestricted and painless motion of the head. In 5 instances there was a mild to moderate degree of limitation, mechanical rather than due to pain or spasm. One patient complained that he suffered from fatigue of the posterior cervical region. This would develop usually after he had been sitting for from three to four hours. In this case there was only 20 degrees extension of the head, and the patient held his head in a slightly flexed attitude. In this instance a portion of the cervical segment of the spine had been fused in a slight degree of flexion, causing an unnatural attitude of the head.

Fusion was reported as solid roentgenographically in 12 cases in from six to twelve weeks after operation. Postoperative roentgenograms were not made in 3 cases, while in 2 instances pseudarthrosis developed. Another patient required further surgical treatment a few weeks after the first operation had been performed. In those cases in which pseudarthrosis developed, repair was not attempted because neither of the patients had sufficient trouble to justify it.

By relieving these patients of preoperative vertebral symptoms of pain, crepitus and spasm, spinal fusion enabled them to move the head more freely than before operation. Also, the feeling of stability which is experienced after fusion of the spine dispels the fear which those patients had of moving the head.

Fourteen patients presented sufficient evidence preoperatively to be classified as having involvement of the nerve roots. Seven had moderate involvement and 7 mild. Two of those who had moderate involvement and 4 of those who had mild involvement preoperatively showed no evidence of irritation of the nerve roots at the follow-up examination, while 5 of those who had moderate involvement preoperatively showed involvement of a mild degree at the follow-up examination, and 3 of those who had mild involvement showed no change.

Ten cases in which preoperative and postoperative roentgenograms were available have been reviewed in connection with the relationship between anterior vertebral displacement and tilt in the presence of involvement of the nerve roots. Five of the patients had anterior displacement of the involved vertebra of from 20 to 8 per cent. Four of these had moderate irritation of the nerve roots preoperatively, while 1 presented no evidence of involvement. On their last visit to the dispensary 2 of the patients were without a nerve root syndrome, while 3 had a mild syndrome. Of 5 others with anterior vertebral displacement of from 0 to 20 per cent before and after operation, 1 had moderate and 4 had mild involvement of the nerve roots preoperatively, while postoperatively and on their last visit to the clinic, the patient with moderate involvement and 3 of those with mild involvement were relieved, while 1 patient still had a mild degree of irritation of the nerve roots.

Seven patients had anterior vertebral tilt of the involved vertebra of from 20 to 58 degrees both preoperatively and postoperatively. Four of these had moderate involvement of the nerve roots preoperatively, while 2 had mild involvement, and 1 had no evidence of injury to the nerve roots. After fusion, the moderate involvement in 2 patients decreased to a mild degree, and 2 of the patients presented no evidence of involvement. The 2 patients with mild involvement preoperatively had no evidence of injury to the nerve roots postoperatively, and the remaining patient was without any involvement, as before operation.

Three other patients had an anterior tilt of the involved vertebrae of from 0 to 20 degrees. One presented evidence of moderate involvement and 2 evidence of mild injury to the nerve roots. The patient who had moderate involvement preoperatively had mild involvement postoperatively; the condition of the patient with mild involvement remained the same, while the other patient did not show any evidence of involvement.

After operation and while these patients were in the hospital there was a definite improvement in the degree of irritation of the nerve roots in some cases. The improvement in the nerve root syndromes was gradual and steady, but after a few months little change was noted.

In comparing preoperative and postoperative roentgenograms, the percentage of anterior displacement and the degree of anterior vertebral tilt in these 10 cases did not change to a great extent. In some instances there was a decrease in the degree of tilt or displacement, while in others an actual increase had taken place. From the fact that so many of these patients were relieved of their nerve root syndrome by spinal fusion, and yet little or no correction of these deformities had taken place, one must naturally suppose that vertebral tilt of a moderate degree, as well as vertebral displacement, if not accompanied by mobility, plays little part in the production of a nerve root syndrome in this type of lesion in its chronic stage.

Six of the patients in the series had a hypermobile luxated vertebra. Two of the patients had moderate involvement of the nerve roots preoperatively, while postoperatively 1 was without involvement, and the other had a mild degree. Two other patients with hypermobile luxated vertebrae had a mild degree of involvement preoperatively and none postoperatively. The remaining 2 patients had neither preoperative nor postoperative involvement. The number of hypermobile vertebrae in this series is small, and yet it may be misleading since the data in regard to gross pathologic changes at operation were very sketchy and incomplete. However, it is interesting to find that 4 of 6 patients with involvement of the nerve roots and with a hypermobile luxated vertebra were either completely or partially relieved of that involvement by spinal fusion. Perhaps the involvement of the nerve roots, which one so often finds as a feature in lesions of the cervical segment of the spine in the chronic stage, may well be explained by the presence of a hypermobile luxated vertebra. Certainly a very mobile vertebra, which is also luxated, can cause a strain on its nerve roots, while the elimination of motion of that vertebra by spinal fusion will produce a mitigation of a syndrome arising from involvement of the nerve roots. It might be assumed that patients in this series who presented such a syndrome but were not aided by spinal fusion did not have a hypermobile vertebra and that sufficient damage to the nerve roots or their coverings had been done at the time of the primary trauma to leave them in a chronically impaired state.

INVOLVEMENT OF THE CORD

Spinal fusion alone was done on 4 patients having involvement of the cord. One of these patients had mild preoperative and postoperative involvement, while another had mild preoperative involvement and severe postoperative involvement. The latter was the one with the severest displacement and tilt of the entire series, and there is no doubt that if, in the presence of such a degree of deformity, laminectomy had been done in conjunction with spinal fusion a far more desirable result would have been obtained. Moderate involvement was present in 1 patient preoperatively and mild involvement postoperatively, while another patient had mild involvement before operation and none after operation.

A one stage laminectomy and spinal fusion were carried out on 5 patients. Two of these had neither preoperative nor postoperative evidence of a syndrome, the laminectomy being done on 1 to remove a very mobile fractured vertebral arch which at any time could have caused severe damage to the cord, while laminectomy was done on the other patient to remove a severely displaced vertebral arch. Laminectomy and spinal fusion were done on 3 other patients with severe involvement of the cord. In 1 of these there was a decided improvement in the cord syndrome, while 1 was relieved to a moderate degree, the remaining patient being slightly improved but still having severe involvement.

As has been mentioned before, the dura was incised at the primary operation in only 1 instance, and yet it was observed in many cases that the dura was thickened. I believe that in the presence of involvement of the cord, when laminectomy is done, the dura should be opened freely if it is at all thickened. An unyielding dura can cause as much pressure on the cord as a pressing vertebral arch, especially in the presence of anterior vertebral displacement or a kyphos.

Table 3.—*Preoperative Status of Patients*

Case	Vertebral Syndrome	Nerve Root Syndrome	Cord Syndrome
1	None	Mild	Severe
2	None	None	None
3	None	Mild	None
4	None	None	Mild
5	None	None	None
6	None	None	None
7	None	Mild	Mild
8	None	None	None
9	None	None	None
10	None	Mild	None
11	None	Mild	Mild
12	None	None	None
13	None	None	None
14	None	None	None
15	None	None	None
16	None	Mild	None
17	None	Mild	Moderate
18	None	Mild	Severe

Laminectomy in 1 case caused a decided improvement in the cord syndrome. By this procedure a severely displaced and fractured vertebral arch was removed. This had caused pressure on the coverings of the cord and on the cord. Neither the presence of a pressing arch nor a fracture of the arch was diagnosed preoperatively.

DISABILITY

The degree of disability of the patients in this series is based on the severity of the cord, nerve root and vertebral syndromes. Preoperatively 3 patients had a severe degree of disability, 13 a moderate degree and 2 a mild degree. Postoperatively, 2 of the patients had a severe degree of disability, 1 a moderate degree and 6 a mild degree, while 9 were without any form of disability. In other words, the results of treatment in 10 cases may be classified as excellent. Nine of the

10 patients having no cord, vertebral or nerve root syndromes had a normal degree of motion in the cervical portion of the spine. One of the patients presented severe involvement of the cord preoperatively, while postoperatively the involvement was of a mild degree. The results in 5 cases were classified as good, i. e., a marked decrease in the severity of the syndromes had taken place. The results in 1 case were fair, while in 2 they were poor. In 1 of the latter cases the patient was much worse than before operation, while in the other case the patient was improved slightly but was still severely handicapped.

In table 3 is given the postoperative status of each patient.

CONCLUSIONS

1. Closed reduction of a fracture-dislocation or dislocation of the cervical portion of the spine in many instances fails to restore the patient to normal.
2. The disability of the patient should be estimated in regard to the degree of involvement of the vertebral column, the nerve roots or the cord.
3. The type of involvement of the cord is difficult to ascertain in a case of a lesion of this nature.
4. An ununited fracture of the vertebral arch is common in such cases and is difficult to diagnose.
5. Natural fusion of the vertebral bodies of the involved vertebra does not occur in a number of cases.
6. Hypermobility of the luxated vertebra is the cause of involvement of the nerve roots in many cases.
7. Spinal fusion of the cervical region is not a dangerous procedure in experienced hands.
8. Spinal fusion is of little value in the treatment of syndromes arising from involvement of the cord, but if possible a combined laminectomy and spinal fusion should be attempted in the presence of involvement of the cord and anterior vertebral displacement.
9. If laminectomy is done, the coverings of the cord should be freely opened if they are at all thickened.
10. Spinal fusion relieves a patient of symptoms referable to the vertebral pathologic processes and is the only adequate means to stabilize a hypermobile luxated vertebra.
11. The mobility of the head and neck is not materially limited by fusion of three or four cervical vertebrae.
12. Anterior vertebral tilt and displacement without mobility play little part in the production of nerve root syndromes.

CLEFT PALATE

A CORRELATION OF ANATOMIC AND FUNCTIONAL RESULTS FOLLOWING OPERATION

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The operation for cleft palate was presented for the first time comprehensively, according to Dorrance, in 1816 by von Graefe, the founder of modern plastic surgery. The operation which is known today as the Langenbeck procedure was described in 1861 by von Langenbeck.

An extensive literature has accumulated since these early operations for cleft palate, and but a small amount of it pertains to the functional results after treatment.

Reports on the phonetic outcome in a group of cases may be satisfactory individually, but great difficulty is encountered in comparing the results in one group with those in another. The difficulties of judging the phonetic results of other investigators arise because, in the first place, the observations made for each report depend on the auditory sense, which is individually variable. Second, there are so many factors involved in speech that a method of anaylsis satisfactory to one observer might not meet the demands of others. Third, the problem of a foreign tongue makes the task of comparison more difficult, for it is probable that certain languages may be more perfectly spoken by a person with a cleft palate.

Ideally, the most accurate evaluation of phonetic results can be obtained only by a trained phoneticist. However, this ideal is difficult to obtain.

The main purpose of this work is to correlate the speech defect with the anatomic result and to make the observations in as simple a manner as possible and by a method which can be carried out by one with no special training in phonetics.

REVIEW OF THE LITERATURE

Whitehead first tabulated the phonetic results in such cases in 1870. Of five patients who had undergone repair for a cleft palate, one had

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Thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

distinct speech, two showed improvement in speech, one had "intelligent speech" but with some nasalization and one wore an obturator.

Bond stated in 1893 that he had never seen a person with a corrected cleft who did not have some speech difficulty.

Kappeler in 1902 stated that it is rare to obtain normal speech without training. Of sixteen patients who did not receive training and did not use an obturator, four had normal speech, one showed noticeable improvement and eleven showed no improvement. Of thirteen who received speech training only, eleven had normal speech, and two showed noticeable improvement. Of twenty-nine who received speech training and also used an obturator, twenty-three had normal speech, and six showed noticeable improvement.

Church in 1904 disagreed with the widely accepted opinion that distinct speech could be acquired by a person with an unrepaired cleft palate.

In 1904 Ranzi and Sultan reported the results in one hundred and one cases. In six, speech was normal; in forty-four, there was improvement; in fourteen, the functional result was not successful; in twelve the operation was unfinished, and in twenty-five, the results were not known.

Berry reported the results in two series of cases. Of the first series of sixty-one cases, reviewed in 1905, he stated: "In no case has speech after operation become absolutely normal, and there are comparatively few in which I should call it very good." According to his data, speech was very good in five cases, good in eighteen, fair in fourteen, indifferent but improving in three, bad in four, already much improved in eight and not yet improved in four. Three of the patients had not yet learned to speak, and no report had been received concerning eight.

In the second group of eighty-one cases, reviewed in 1911, he stated that there were some cases in which speech was so nearly perfect that it was difficult to detect anything wrong. The results are tabulated separately for individual cases. An analysis shows that the results are apparently more favorable than those in the previous series.

Brown in 1908 stated that the ultimate result is measurable only by the perseverance by which continued speech training is received. He noticed that the parents of many children with cleft palate had some speech defect which may have been either a nervous inefficiency in speech mechanism or a slight imperfection of anatomic development, either of which became a cleft in the next generation. He also stated that scars of the lips disturbed the articulation of b, f, m, p, v and w and that in many cases the articulation of c, d, g, h, j, k, l, n, r, s, t and z was poor because all of these sounds, which are uttered by the tongue behind the teeth, were distorted by an imperfect arch and teeth caused by ill advised operations in infancy.

Blakeway stated, in comparing results of different operations in 1914, that of seventeen persons operated on by the Lane technic there were five who were old enough to speak, and all of these were poor speakers.

Brophy stated in 1914 that "if operation is properly performed early, no defect is noted in phonation." He also stated that if operation is performed between the ages of 2 and 12 more or less defect in speech will remain unless the patient is properly trained by one who understands speech.

Stahl in 1923 reported the following results in thirty-one cases: In ten speech was perfect; in eight, good; in seven, fair; in two poor, and in four, very poor.

Monnier reported the results in ninety-three cases in 1924. In twenty-two speech was good; in thirty-four, good with slight nasalization; in fifteen, distinct with marked nasalization, and in twelve, indistinct, while in ten the patient had not yet learned to speak.

Barrington-Ward in 1927 reported that speech was good in twenty of fifty-seven cases, fair in eighteen and bad in twenty. Four of the persons with bad speech were mentally defective.

Tschmarke reported normal speech in 9.1 per cent of forty-five cases, improved speech in 57.6 per cent and unimproved speech in 33.3 per cent. He presented the following tabulation in which are compared the percentage of well healed palates and the satisfactory functional results obtained by different authors:

Author	Healed Palates %	Satisfactory Functional Results %
Kappeler	86.5	53.3
Ranzi and Sultan	69.3	9.3
Stahl	58.7	15.0
Veau and Ruppe	74.0	25.0
Dreher	60.9	34.7
Tschmarke	64.3	9.1

Turner stated that of forty-four cases in which the palate was completely restored, speech was normal in seven, good in twenty, fair in fourteen and bad in three.

Halle stated that in most instances if operation is performed in the first year speech will be normal or almost normal.

Nitch in 1927 obtained good speech in thirteen of thirty-five cases, poor speech in seventeen and bad speech in five.

Burdick in 1930 remarked that no matter how successful an operation is and no matter what type of operation is performed the speech will be far from normal. He obtained good results in nine of twenty-three cases of incomplete cleft and in six of twenty-two cases of complete cleft.

Pagnamenta in 1932 tabulated his anatomic and functional results. These are presented in table 1.

In 1929 Veau reported the phonetic results in one hundred cases cases in which the classic procedures of Langenbeck or one of its modifications was used. The speech of ten of the patients improved rapidly, and they spoke well or nearly normally: the speech of six was improved by phonetic education and presented little, if any, defect. Twenty-four of the patients had poor speech with little intelligibility.

In 1922 Veau reported the ultimate functional results of forty in which his procedure was used. Thirty-five per cent of the patients had normal phonation; 29 per cent had good speech but with nasal air and bad nasalization, and 36 per cent had vocal deficiency in that they were unable to produce certain sounds such as p, t and k or ch, s, j and z.

In 1933, in a second series of one hundred cases, he found 62 per cent of the patients with normal speech, 23 per cent with the nasal air and nasalization and 15 per cent with vocal deficiency.

TABLE 1.—*Anatomic and Functional Results of Pagnamenta*

Type of Cleft	Number of Cases	Good Palates, %	Understandable Speech, %	No Nasalization, %	Slight Nasalization, %	Severe Nasalization, %
Partial cleft	27	55	77	29	14	5
Subtotal cleft	48	39	63	21	46	33
Total unilateral cleft with lip defect	54	30	55	15	43	42
Total bilateral cleft with lip defect	16	23	42	0	35	65

Throughout all his work Veau stressed the fact that a good anatomic result is essential for a good functional result regardless of speech training. Of one group of forty patients with normal speech, twenty-four had had no speech training. Of the sixteen who had to be reeducated, fifteen spoke before operation.

Other articles, by Veau and Borel, and Ruppe and Ruppe, give their methods for analyzing and training of speech.

MECHANISM OF CLEFT PALATE SPEECH

There are two main characteristics of speech which are noted in practically all cases of cleft palate: (1) disturbed quality of tone and (2) disturbances of articulation.

1. A disturbed quality of tone is exemplified by what is commonly known as "nasalization," "nasaling," "nasal tone" or "talking through the nose." The term nasalization will be used in this analysis. It is also exemplified by a lack of what is usually termed "resonance" and also of "inflection," thereby giving the flat, uninteresting monotone so characteristic of the person with a cleft palate.

The following is an interpretation of this disturbed quality of tone after a study of the current texts on speech and voice:

After a column of air which has been put into motion by the lungs, intercostal muscles, diaphragm and abdominal musculature passes through the larynx, it emerges with a sound which has two characteristics, pitch and intensity.

The pitch is determined by the number of vibrations of the vocal cords and is the result of a fundamental tone plus a range of overtones or undertones, called partials. Ordinarily the ear is not aware of these partials, as they, together with the fundamental tone, are heard as one sound with a definite pitch.

When the column of air, which now has pitch and intensity, reaches the pharyngeal, oral and nasal cavities, it enters into "resonating" cavities. These cavities have the power to set up vibrations which differ according to their size and shape. The number of vibrations may equal the vibrations of the fundamental tone, in which case this tone is augmented; or the number of vibrations may equal those of one of the partials, in which case that particular partial is augmented, or a number of different vibrations may be set up at the same time augmenting a combination of partials. The result of this modification of the original tone by the vibrations set up in the upper respiratory passage adds a third characteristic to the original tone, a quality or timbre.

This addition of quality is well demonstrated by Bell:

> Press your lips firmly together while you blow air between them, so as to cause the edges to vibrate. The sound produced is not very pleasant and resembles, more than anything else, the hum of a bee . . . . But place the buzzing lips at the end of a tube, for example, a trumpet, and at once the quality changes . . . . In this case the source of the sound is found in the vibration of the lips but the timbre or quality is due to the trumpet.

Any change in the resonating cavities of the upper respiratory passages will change the quality of a sound.

There are three main defects in these cavities in cases of cleft palate which tend to change the quality of a sound.

(*a*) The first is defective closure of the velopharyngeal sphincter. This defect permits the column of air to be shunted away from the normal resonating chamber, the mouth, to an abnormal one, the nose. It not only gives the flat monotone speech characteristic of a person with a cleft palate but also is the cause of nasalization. This deformity is by far the most serious of the three defects and the resulting quality of sound is called rhinolalia aperta.

(*b*) Changes in the size and shape of the chambers, giving an abnormal nasal resonance, is the second cause of defective quality of speech. Nasal resonance of some degree is a part of *all normal* speech and is acquired by vibrations set up in the nasal cavities by the column of air below the closed velopharyngeal sphincter transmitting its impulses through the soft palate, thus adding a nasal quality to the resultant tone. That the patient with a cleft palate usually has a nasal passage of abnormal size and shape is commonly recognized. This abnormality is most frequently a narrowing of the nasal cavities, by a deformed septum, enlarged turbinates or enlarged adenoids. The resulting defect in quality of sound is called rhinolalia clausa and is exemplified in a person who has a cold.

Cleft palate speech, which is usually characterized by both of the aforementioned defects in quality, rhinolalia clausa and rhinolalia aperta, is designated as rhinolalia mixta.

(*c*) The third anatomic defect which may disturb the quality of a tone is less important but must play some rôle, although it is impossible to analyze it separately. This defect consists of the scar tissue and taut mucous membrane surfaces which result from the operation and which undoubtedly hinder the vibrating property of these surfaces.

2. Disturbances of articulation, the second characteristic of speech noted in the majority of cases of cleft palate, has been well summarized by Hudson Makuen. According to him, normally consonants are made

> . . . by impeding the column of air of breath at certain points above the larynx. The points at which this impediment takes place are called the stop positions. These have been divided into the anterior, middle and the posterior stop positions. The anterior one is formed by the lips (in the articulation of the so-called labial sounds, p, b, m, wh, w), by the lower lip and teeth (in the articulation of the labiodentals f and v) and by the tip of the tongue and teeth (in the articulation of the linguo-dentals th and ch); the middle one by the tongue and the hard palate (in the articulation of the anterior-linguo palatals s, z, sh, t, d, n, l); and the posterior one, by the dorsum of the tongue and soft palate (in the articulation of the posterior linguopalatals r, g, h, y). For all these sounds requiring an impediment in the outgoing column of breath, whichever stop position may be used, it is necessary to have a freely movable and normal palate.

In the cleft palate which has not been repaired, the anterior and middle stop positions are rarely used because of the inability of the patient to focus his vocalized breath at this point when there is a free passage for air through the nasal cavity. The patient uses substitute stop positions, such as the anterior nares, the base of the tongue and the posterior pharyngeal wall and the lips of the larynx formed by the arytenoid cartilages and the arytenoid and aryepiglottic folds.

When perfect closure of the velopharyngeal sphincter is obtained after operation, this habit of using substitute stop positions is one of the major causes of poor speech.

ANATOMIC CONSIDERATION

Dorrance, Whillis and Wardill have presented this subject with special emphasis on the sphincteric action of the muscles of the soft palate and the posterior pharyngeal wall.

The "velopharyngeal sphincter" is a well established entity, and hereafter insufficient approximation of the soft palate with the posterior pharyngeal wall will be described as velopharyngeal insufficiency.

MATERIAL AND METHOD OF USE

This report concerns one hundred cases of cleft palate in which an operation was done for repair.

The records of seventy-five cases were obtained from the files of Dr. H. P. Ritchie. Those of thirteen cases were obtained from the files of the Special Class Department of the Minneapolis Board of Education and concern children who had had speech training in the city schools at one time or another. The data on the remaining twelve cases were obtained at the University of Minnesota Hospital Dispensary as the patient returned for a routine check on his condition. All patients observed were used for this study except a few who were too young to cooperate or those who refused to talk.

The greater portion of the patients were operated on by Dr. H. P. Ritchie or by one of his associates. The type of operation has not been recorded in the study of each case. However, the majority of persons were operated on by the fundamental Langenbeck procedure with suturing of raised mucoperiosteal flaps in the midline, muscle suture of the soft palate with a figure of eight suture and occasional wiring of the premaxilla, as described by Ritchie. In the last few years the wiring of the alveolar process has been discontinued, except in cases in which the defect is of unusual degree, and instead the lip is repaired as a preliminary procedure to mold the alveolar process by muscle pull.

The sounds and words used in the phonetic outline have been suggested by Dr. Bryngelson, of the University of Minnesota Speech Clinic, and are taken from his outline on articulatory speech disturbance, which is a modification of the Travis-Rasmus speech sound discrimination tests.

All of the cases were grouped in the manner suggested by Davis and Ritchie in 1922, which is briefly:

Group I.	Lip cleft.
Group II.	Palate cleft (normal lip and alveolar process), designated according to the length of the cleft of the hard palate as 1/3, 2/3 or 3/3 and cleft of the soft palate only.
Group III.	Lip, alveolar process and palate cleft, designated as right, left or bilateral and complete or incomplete, i. e.: Right complete or right incomplete Left complete or left incomplete Bilateral complete or bilateral incomplete

TABLE 2.—*Outline Used For Analysis of Phonetic Results After Operation in Cases of Cleft Palate*

Father's name.................................... Address..
Patient's name.................................... Birth date....................Age.................
Patient's group.................................... Hospital and record number....................
Phonetic education...

I. Lip:
  Form........................ Operation date........................ Interval.................
  Examination: 1. Nostrils: Contour...
    2. Body of lip: Looks........................... Motion..........................
    3. Speech:

Letter	Initial	Medial	Final	Result
O	old			....
	so			....
	The old oak stood so much alone			....
U	unit			....
	use			....
	Few argue and use cues as fuel			....
B	base	may be	cab	....
	Baby Bee bit her boots			....
P	pay	paper	ape	....
	Paul slipped on a potato peel			....
M	May	camel	same	....
	May made mama maim the man			....
V	vain	ivy	save	....
	Veal was divided in five parts			....

Comment: ....
....

II. Process:
  Form Operation date
  E
    2. Speech:

Letter	Initial	Medial	Final	Result
T	tail	city	sit	....
	Tom ate ten tomatoes			....
D	do	daddy	fade	....
	Fido is Freda's poodle			....
Ch	chart	catcher	patch	....
	The pitcher changed his church			....
Th	then	others	path	....
	Then the path of others was strengthened			....

Comment: ....
....

III. Palate—Hard:
  Form........................ Operation date........................ Interval.................
  Examination: 1. High..................... Median..................... Low..................
    1. Speech:

Letter	Initial	Medial	Final	Result
Y	year	yoyo		....
	Yale men yelped at the Yeoman			....

Comment: ....
....

IV. Palate—Soft:
  Form........................ Operation date........................ Interval.................
  Examination: 1. Anatomy:
    a. Uvula..
    b. Motility: 1.............. 2.............. 3.............. 4..............
    c. Texture: Full........................ Soft..........................
      Thin........................ Hard..........................
    d. Approximate length.................... Long..........................
      Median..........................
      Near..........................
    e. Approx. dist. to post. pharyngeal wall.............................
      Long..........................
      Median..........................
      Near..........................
    f. State when "Ah"
      Approx. dist. to post. pharyngeal wall.............................
      Long..........................
      Median..........................
      Near..........................
      Superior constrictor muscle...
        Well developed.............. ....
        Undeveloped...
      Insertion of levator...
        Prominent...
        Not prominent...

TABLE 2.—*Outline Used For Analysis of Phonetic Results After Operation in Cases of Cleft Palate—Continued*

2. Functional:
   a. Functional test..
   ....
   b. Speech:

Letter	Initial	Medial	Final	Result
K	cape	ache	racket	....
	Keep cool if you can			....
G	get	agony	lag	....
	The rogue stole the goose			....
Ng		slinging	hang	....

Comment: ....
....

General Impression: Anatomic Result:
Lip..
Process..
Palate (hard)..
Palate (soft)..
Functional Result..
....

Table 2 presents the type of outline used in each case.

It has been the purpose in this study to follow the suggestion of the classification of Davis and Ritchie and take up each cleft separately, viz., the lip, the alveolar process, the hard palate and the soft palate, and to choose sounds which are made for the most part by these structures and from which any deviation from the normal can easily be ascertained.

For the lip itself, b, p, and m are used. O, u and v were also used, although not true labials, because the lip is used in a different manner than b, p and m.

For the alveolar process, sounds classified not only as linguodentals, such as ch and th, but as anterior linguopalatals, such as d, t and s, were used. The latter are used in the test for the alveolar process instead of for the hard palate because they are articulated at the junction of the alveolar process and the hard palate.

For the hard palate, y (j) was the sound used. Reference was also made to the anterior linguopalatals of the preceding group.

For the soft palate, k and hard g as well as ng were used. In this analysis the anatomic study was more comprehensive. The motility was graded in degrees from 0 to 4, the latter being that of a normal palate.

No accurate measurements by linear scales were made. Estimations of the length of the repaired palates were recorded. After fifty of these had been recorded, the average length was estimated. Those palates of average length were recorded as normal; those longer than average were recorded as long, and those shorter than average were recorded as short.

The same procedure was carried out for the estimations of the distance from the palate to the posterior pharyngeal wall in the quiescent state and also when "Ah" was said.

Comparisons were not with the normal palate. Similar estimations on twenty-five normal palates indicated that the average length of the normal palate was longer than that of the cleft palate, and the average distance to the posterior pharyngeal wall both in the active and in the quiescent state was shorter in the normal than in a cleft palate. Consequently, when a cleft palate was designated as long, it was long as compared to the average length of a group of cleft palates and not to the length of a normal palate.

The consistency of the soft palate as well as the development of the superior constrictor muscle and the prominence of the insertion of the levator muscles were also recorded.

The functional test used in the majority of cases was performed as follows: A small piece of rolled paper was placed on the surface of each of two pieces of cardboard, measuring about 3 by 2 inches. One of these was held just above the vermilion border of the upper lip and the other just below the vermilion border of the lower lip. The patient was then told to blow the piece of paper off the lower one. If any air escaped through the nose, the piece of paper on the upper cardboard also moved or was blown off the card, showing that there was incompetent closure of the velopharyngeal valve.

ANALYSIS OF MATERIAL

The purpose of this analysis, as previously stated, is to determine to what degree and manner the anatomic defect influences the functional result after operation.

One hundred cases were studied. Seventy-seven were classified as belonging to group III. In fifteen of these the cleft was bilateral, and in sixty-two, either right or left unilateral. In two of the fifteen cases of bilateral cleft the palate was normal. Twenty-three cases were classified belonging to group II. Twenty of these were placed either in group II 1/3, group II 2/3 or group II 3/3. Only three were classified as belonging to group II, cleft of the soft palate only.

The sounds used for the analysis were the consonants, except in one instance, in which o and u were used. The phonetic defect of these consonants is usually made up of two elements. The first is a result of insufficient closure of the velopharyngeal sphincter, resulting in nasalization. The second is the articulatory defect, which may be the result of nasalization but to which is added the defect caused by an anatomic fault at a stop position.

In every case an attempt was made to establish the relative importance of insufficient closure of the velopharyngeal sphincter and the anatomic stop position.

Correlation as Regards Defects of the Lips.—The lip is the labial portion of the anterior stop position. B, p, m, v, o and u were the sounds used. This part of the study included only the cases in group III, in which the clefts were bilateral or unilateral and complete or incomplete. In none of the cases in group II was there an anatomic defect of the lips.

Whether the phonetic defect was in the initial, medial or final stop position is designated by numerals 1, 2 and 3. A defect of an initial p is designated as p 1, of a medial p as p 2 and of a final p as p 3. The same procedure is used throughout for all the stop positions, whether the lips, the alveolar process or the palate are being studied.

An analysis of the phonetic results in those cases in which there was a defect of the lip is given in table 3. A discussion of this table follows:

B 1 was absent in one case (67) and faint in another (21), while p 1, 2 and 3 was omitted in one case (37). There was some degree of nasalization in all these cases, and as the main cause for omission of sounds is inability to focus the air on the correct stop position, due to imperfect closure of the velopharyngeal sphincter, this nasalization rather than the anatomic defect of the lip can be held responsible for the phonetic defect.

B 1 and p 1 were articulated through the nose in one case (33). There was no anatomic defect of the lip in this case, but nasalization of 2 degrees was the cause of the phonetic defect.

U 1 was slightly indistinct in one case (15). The function of the lips was good in this case, but there was nasalization of 4 degrees, which in all probability caused this defect.

The most common defect was the substitution of b for p, m for p or m for b. In all of these cases except case 29, there was some degree of nasalization. With nasalization present, the tendency is to use the sound which is made by a similar architecture of the stop position but which requires less perfect closure of the velopharyngeal sphincter.

In one case (29) there was no anatomic defect of the lip and no nasalization, yet the patient substituted m for b 1. The record of this case showed that the patient talked perfectly if the speech was slow and that the phonetic defect occurred only when the speech was rapid. This demonstrates the occasional case in which there is perfect anatomic function but the patient has not developed the power to move the soft palate rapidly.

In view of the results of this analysis, the conclusion is that as far as the labial element of consonants is concerned the patients in group III can adequately compensate for any anatomic defect of the repaired lip.

Correlation as Regards Defects of the Teeth, Alveolar Process and Extreme Anterior Part of the Hard Palate.—The linguodentals, such as th, ch and s, and the anteriolinguopalatals, t and d, were employed in this analysis. There were four types of functional defects and fourteen variations of anatomic defects. The number of functional defects outnumbered the anatomic defects, as there were two separate types of functional defects in twelve cases. Thus the totals have no reference to the number of cases (table 4).

1. Slur of ch or s or both. The recording of this defect was the most difficult of all, for if one critically analyzes a group of normal persons, the probabilities are that a slight slurring element will be found in many of them on the articulation of the sibilants.

TABLE 3.—*Analysis of Functional Defects in Relation to Anatomic Defects of the Lips*

Case	Anatomic Defect	Functional Defect	Nasalization, Degree
9	Short lip	None	0
13	Short lip	None	0
23	Short lip	None	0
34	Short lip	p 1 = b 1	3
57	Short lip	None	2
15	Abnormal scar	u 1, slightly indistinct	4
22	Abnormal scar	None	2
24	Abnormal scar	b 1 = m 1	1
40	Abnormal scar	None	2
55	Abnormal scar	None	—1
63	Abnormal scar	None	1
20	Muscle out of contact	None	2
62	Muscle out of contact, large hole in hard palate also	b 1 = m	1
26	Tight lip	None	1
59	Tight lip	None	1
37	Notch in vermilion border	p 1, 2, 3 omitted	1
46	Notch in vermilion border	None	0
53	Notch in vermilion border	None	0
41	Poor motion	None	0
67	Poor motion	b 1 = m, b 1 omitted	3
8	No anatomic defect	p 1 = b 1	1
21	No anatomic defect	b 1, faint	1
29	No anatomic defect	b 1 = m	0
33	No anatomic defect	v 1 = b; b 1 and p 1, through the nose	2
60	No anatomic defect	b 1 = m	3
61	No anatomic defect	b 1 = m	2
93	No anatomic defect	b 1 = m	1

In forty-two of the sixty-five cases, or 64 per cent, there was some degree of slurring of ch or s. In some cases it was extremely difficult to determine whether there was a sufficient degree of slurring to class it as a defect, but if there was the slightest question it was recorded as such.

This defect, although the most frequent, is by far the least important as far as the general speech of the patient is concerned. In fourteen of the forty-two cases, or 25 per cent, in which the results in regard to speech were ultimately classed as excellent, this defect of slurring of ch or s was so slight that there was no hesitation in classifying the results as excellent.

The question as to whether the anatomic defect of the stop position has more influence on this functional defect than the degree of velopharyngeal insufficiency is difficult to determine.

The fact that in thirty of the forty-two cases, or 71 per cent, some degree of velopharyngeal insufficiency was present would lead one to conclude that the latter element is an extremely important one.

On the other hand, it was noted that the degree of nasalization was minimal in practically all of these cases. As only a moderate force is needed to articulate a good ch or s, it is quite possible that perfect closure is not absolutely necessary for a good ch or s and that a minimal degree of nasalization plays no rôle in slurring of ch or s.

Table 4.—*Incidence of Functional and Anatomic Defects*

Functional Defects	Incidence
1. Slur of ch, s, or both	42
2. Ch or s or both spoken through the nose	10
3. Omission of s, *ch* 1, 2, 3; d 1, 2, 3 or t 1, 2, 3	15
4. Substitution: d = n, t= d = n, s = n	5
5. Absence of functional defect; anatomic defect	5
Total	77
Anatomic Defects	
1. Atrophied premaxilla	2
2. Malocclusion	4
3. Notch in alveolar process	4
4. Orthodontia	8
5. Teeth out of line	16
6. Tooth misplaced posteriorly	5
7. Tooth misplaced anteriorly	1
8. Teeth abnormally spaced	4
9. Small hole anterior to alveolar process	8
10. Overlapping of medial with lateral process	4
11. Overlapping of medial by both lateral processes	1
12. Teeth in poor [illegible]	1
13. Short process, [illegible]	2
14. No teeth present	1
15. Absence of anatomic defect; functional defect	4
Total	65

Furthermore, the contour of the teeth plays an important rôle in the articulation of the sibilants, and as the greatest number of cases of defective articulation were observed in persons in whom the contour of the teeth was defective, the probabilities are that a defective contour and not defective closure of the velopharyngeal sphincter was responsible for a slur of ch or s.

The fact that one observes this functional defect in many normal children who have an extremely irregular contour of teeth strengthens this impression.

Thus one concludes that the anatomic defect of the teeth and the alveolar process is responsible for slurring of ch or s and that defective closure of the velopharyngeal sphincter plays no rôle.

2. Ch or s or both spoken through the nose. There were ten cases in which this defect was present, and in nine some degree of

nasalization was present. In the one case in which no velopharyngeal insufficiency was present there was a small hole anterior to the alveolar process which may have been the cause of the defective articulation.

In two of the cases there were holes in the anterior part of the hard palate. Holes in the anterior part of the hard palate tend to cause an omission of sounds rather than articulation through the nose, as will be demonstrated in the analysis of persons with defects of the hard palate. Therefore, in these two cases the defect was more than likely due to velopharyngeal insufficiency rather than to the holes in the hard palate.

The anatomic defects in this group of cases were as follows: an atrophied premaxilla, one case; malocclusion, one case; orthodontia, two cases; teeth out of line, two cases, and a tooth misplaced posteriorly, one case. In one case there was no anatomic defect of the process but a marked degree of velopharyngeal insufficiency.

As no type of defect of the alveolar process was consistently found in the persons who articulated s or ch through the nose and as velopharyngeal insufficiency was consistently found, the probabilities are that the poor function of the velopharyngeal sphincter was responsible for the phonetic imperfection of articulating ch or s through the nose rather than any anatomic defect of the alveolar process.

3. Omission of s, d, ch or t. There were fifteen cases in which this defect was present. The anatomic defects were as follows: malocclusion, two cases; teeth out of line, four cases; a tooth misplaced posteriorly, one case; teeth abnormally spaced, one case; a small hole anterior to the alveolar process, two cases; overlapping of the medial with the lateral process, one case, and overlapping of the premaxilla by a tooth, one case.

In fourteen cases, or 93 per cent, there was some degree of velopharyngeal insufficiency. In six cases there were holes in the hard palate, besides, the majority being in the anterior part of the hard palate or extending into it.

In one case in which there was no nasalization, the patient had no difficulty with the labial or soft palate consonants, and therefore the probabilities are that the phonetic defect present was due to incorrect habits acquired before operation. The fact that the operation had been performed only six months before this analysis strengthens this impression.

No consistent anatomic defect was found in the alveolar process, whereas velopharyngeal insufficiency was common to all except the one mentioned. This would tend to show that the defect in the alveolar process was not responsible for this phonetic defect but that the inability to close the palate sphincter was the cause.

The question whether or not the omission of these consonants in the six cases in which there were holes in the hard palate was due to these holes or velopharyngeal insufficiency is difficult to determine. Holes in the anterior portion of the hard palate often cause omission of these consonants. These holes were present in only six cases, whereas velopharyngeal insufficiency was present in fourteen. Thus, there were eight cases in which the only anatomic defect was incompetency of the velopharyngeal sphincter.

The impression is that in the omission of the anterior linguopalatal sounds velopharyngeal insufficiency is responsible rather than a defect in the alveolar process unless a hole is present in the hard palate, in which case both anatomic defects are probably responsible. The velopharyngeal defect is possibly the more important of the two.

4. Substitution—d=n, t=d=n, s=n. There were five cases in which this phonetic defect was observed. In all there was some degree of velopharyngeal insufficiency.

As was the case in the articulation of the labial consonants, the consonants requiring less perfect closure of the velopharyngeal sphincter were substituted.

In general, therefore, in persons with defects of the alveolar process velopharyngeal insufficiency plays the major rôle in articulation of the consonants, except the sibilants, in which case the anatomic defect of the alveolar process is more important.

Correlation as Regards Defects of the Hard Palate.—There were twenty-one cases in this group. In fourteen there was no functional defect. In the seven cases in which there were both functional and anatomic defects, four of the patients omitted one or more of the consonants, two spoke the consonants indistinctly and one substituted. All had some degree of nasalization.

Of the twelve cases in which small holes from 1 to 2 mm. in diameter were found in the hard palate phonetic defects were noted in only two. In one case (34) the patient substituted t 1 for d 1. Velopharyngeal insufficiency of 3 degrees undoubtedly was the cause of this defect. In the other case (74), the patient pronounced y indistinctly. Nasalization of 1 degree may have been the cause for this.

In one case (62) a large hole was present in the anterior part of the hard palate, yet in some way the patient articulated all the consonants extremely well. The impression was that the tongue was used to plug the defect.

In one case (91) there were two large holes, one on each side of the palate where lateral incisions had been made. Each hole was 1 by 1 cm. in diameter. The phonetic defect present was a mixture of the more common nasalization plus a quality which is noticed in one who attempts to talk with hot food in the mouth. This "hot food" quality was also noted in case 63.

In one case (61) a hole measuring 1 by 1 cm. was present at the junction of the hard and the soft palate. All the initial consonants, including k and g, were omitted. Nasalization of 2 degrees was also present, which may have accounted for the omission of the anterior and middle stop position consonants but possibly not for the posterior stop position sounds, k and g.

In two of the four cases in which the patient omitted the consonants there were holes in the anterior part of the palate and in two there were holes in the posterior part of the hard palate.

TABLE 5.—*Analysis of Functional Results in Relation to Anatomic Defects of the Hard Palate*

Case	Anatomic Defect	Functional Defect	Nasalization, Degree
2	Hole, midpalate, 1-2 mm.	0	0
5	Hole, midpalate, 1-2 mm.	0	0
12	Hole, midpalate, 1-2 mm.	0	0
19	Hole, midpalate, 1-2 mm.	0	0
21	Hole, midpalate, 1-2 mm.	0	1
30	Hole, midpalate, 1-2 mm.	0	2
34	Hole, midpalate, 1-2 mm.	t 1 = d 1	3
46	Hole, midpalate, 1-2 mm.	0	0
49	Hole, midpalate, 1-2 mm.	0	0
53	Hole, midpalate, 1-2 mm.	0	0
74	Hole, midpalate, 1-2 mm.	Indistinctly	1
43	Hole, midpalate, 1-2 mm.	0	0
61	Hole, 1 by 1 cm., junction of hard and soft palate	Omits all initials	2
62	Hole, 2 by 1 cm., anterior part of palate	0	1
63	Hole, 3 by 1 cm., anterior part of palate	Omits d 1, 2, 3	1
80	Hole, 1-2 mm., anterior part of palate	Indistinct d 1, 2, 3 th 1, 2, 3	2
91	Two holes, 1 by 1 cm. on each side	0	2 plus "hot food sound"
52	Hole, 1 cm., anterior part of palate; hole, 1 cm., midpalate	t 1, 2, 3 d 1, 2, 3 } omitted	1
35	*Nasal mucous membrane present in arch*	*y 1 omitted*	1
69	Abnormal scar	0	1
95	Hole, 1-2 mm., junction of hard and soft palate	0	1

In one case (80) in which there was a small hole in the anterior part of the palate, the patient articulated d 1, 2 and 3 and th 1, 2 and 3 indistinctly.

From the statistics alone it is rather hazardous to draw conclusions. A defect of the velopharyngeal sphincter was common to all the cases in which there were phonetic defects, but it was also present in a majority of the cases in which phonetic defects were not present. It is the general impression that when a large hole is present in the hard palate, defective closure of the velopharyngeal sphincter is a minor cause of the phonetic defect in spite of the greater constancy of velopharyngeal insufficiency in all of these cases. Omission of the anterior linguopalatals is apparently the more common phonetic defect of large holes of the palate, especially if the holes are in the anterior part of the hard palate or extend into it. Holes in the lateral part of the hard palate cause a "hot food" quality to be added to the usual nasalization and cause little or no defect in the articulation of the consonants. Small holes in the middle part of the hard palate cause no articulatory dysfunction.

Correlation as Regards Defects of the Soft Palate.—In this analysis there was a hole in the soft palate in only one case (61). This was large, and in spite of nasalization of 2 degrees it probably was the cause of the omission of the initial k and g.

As for the remainder of the cases, the most important factors seemed to be the motility and length of the soft palate. Consequently, in table 6 the cases in which phonetic defects were present are classified according to the length and motility of the soft palate. The number of cases in which the soft palate was of the same motility and length but in which there were no phonetic defects referable to the soft palate are included for comparison.

The relative importance of length, motility and texture of the soft palate as regards closure of the velopharyngeal sphincter was estimated.

The most common defect in this group was omission of soft palate consonants. A certain degree of velopharyngeal insufficiency, as evidenced by the degree of nasalization, was present in every case except one, and in this one there was merely a slurring of k.

There were phonetic defects referable to the soft palate in nineteen of ninety-seven cases in this group. Three cases were not used in this analysis because two belonged in group III, with clefts of the lip and the alveolar process and normal palates, and there were insufficient data on one.

There can be little doubt that the phonetic dysfunction in these cases was dependent almost entirely on the amount of velopharyngeal insufficiency, granting that there was no hole in the soft palate, as in case 61 in which the hole also played an important part.

Relative Importance of Length, Motility and Texture of the Soft Palate in Closure of the Velopharyngeal Sphincter.—Closure of the velopharyngeal sphincter is dependent on the motility, length and texture of the soft palate. Of the patients with soft palates with motility of 4 degrees, 5.8 per cent (one of seventeen) were defective as far as articulation of soft palate sounds was concerned. Of those with palates with motility of 3 degrees, 16 per cent (seven of forty-two) were defective; of those with palates with motility of 2 degrees, 16.6 per cent (three of fifteen) were defective; of those with palates with motility of 1 degree, 28 per cent (four of fourteen) were defective, and of those with palates with no motility, 50 per cent were defective.

Thus, as the motility decreases, the number of cases of defective articulation increase.

As far as length is concerned, 7 per cent of the patients with long palates had defective articulation of soft palate consonants; 17 per cent of those with median palates had this phonetic defect, and 37 per cent of those with short palates were thus affected.

TABLE 6.—*Analysis of Phonetic Defects in Relation to Anatomic Defects of the Soft Palate*

Case	Motility	Texture*	Length†	Nasalization	Phonetic Defect	Normal Palates with Same Motility and Length But No Phonetic Defects
17	4	F. S.	M	1	k 1, 2, 3 slurred	
	4	F. S.	L	..	....	
	4	F. S.	S	..	....	
Total 1						Total 16
14	3	F. S.	L	0	k 1 indistinct	
35	3	F. S.	L	1	k 1; g 1 omitted	
Total 2						Total 12
33	3	F. S.	M	2	k 1, 2, 3 slurred; g 1, 2, 3 indistinct	
21	3	F. S.	M	1	k 1; g	
23	3	F. S.	M	1	k 1, 2, 3 omitted	
90	3	F. S.	M	2	k 1, 2, 3 omitted; g 1 omitted	
Total 4						Total 12
37	3	F. S.	S	1	k 1, 2, 3 omitted	
Total 1						Total 11
60	2	F. S.	M	3	k 1, 2, 3 omitted	
71	2	T. H.	M	1	k 1, 2, 3; g 1, 2, 3 omitted	
Total 2						Total 9
20	2	F. H.	S	2	k 1, 2, 3; g 1, 2, 3 omitted	
Total 1						Total 2
..	2	F. H.	L	..	....	
Total 0						Total 4
73	1	T. S.	S	3	k 1, 2, 3; g 1, 2, 3 omitted	
77	1	T. S.	S	1	g 1 = y	
86	1	T. H.	S	1	k 1, 2, 3; g 1, 2, 3 omitted	
67	1	F. H.	S	3	k 1; g 1 omitted	
Total 4						Total 1
..	1	T. S.	M	..	....	
Total 0						Total 6
..	1	T. S.	L	..	....	
Total 0						Total 3
61	0	T. H.	S	2	k 1; g 1 omitted	
62	0	T. H.	S	1	k 1, 2, 3; g 1, 2, 3 omitted	
78	0	T. H.	S	3	k 1, 2, 3; g 1, 2, 3 omitted	
Total 3						Total 0
..	0	T. H.	L	..	....	
Total 0						Total 0
..	0	T. H.	M	..	....	
Total 0						Total 3
56	..	T. S.	L	2	k 1; g 1 omitted	
Total 1						Total 0
19						79

* F. S. indicates full and soft; T. S., thin and soft; F. H., full and hard, and T. H., thin and hard.

† L indicates long; M, median and S, short.

As far as length and motility are concerned, one can make no definite statement concerning their relative importance from the statistics alone, but the general impression is that a person with a short palate with good motility has a better chance of good function of the velopharyngeal sphincter than one with a long palate with no motility. An analysis of the whole group of one hundred cases, including those in the group which have just been analyzed, brings this out also. The results show that 50 per cent of the patients with long palates, 69 per cent of those with median palates and 54 per cent of those with short palates had nasalization, while 55 per cent of those with palates with motility of 4 degrees, 62 per cent of those with palates with motility of 3 degrees, 64 per cent of those with palates with motility of 2 degrees, 81 per cent of those with palates with motility of 1 degree and 100 per cent of those with palates with no motility had some nasalization.

Motility seems to be the more consistent as regards the presence of velopharyngeal insufficiency.

As regards the consistency of the soft palate and its effect on articulation, it can be concluded that while it has no effect per se it has an effect secondarily by its relation to motility. The average motility of the full, soft palates is 3; that of the thin, soft palates is 2; that of the full, hard palates is 1.5, and that of the thin, hard ones is 1.1.

Motility is therefore of more importance than length, although the latter is of marked importance for competent closure of the velopharyngeal sphincter. As far as can be determined, little emphasis has been given to possible injury to the nerve supply of the palatal muscles by the different types of operations. No description of the course and distribution of the nerves supplying the tensor veli palatini or the levator veli palatini muscle has been found. It seems of great importance as far as preservation of motility is concerned to demonstrate their course if possible and to ascertain the danger of injuring them in the different types of operation for repair of the soft palate.

Superior Constrictor Muscle.—That the superior constrictor muscle elements are well developed in cases of cleft palate is evident. In this series 88 per cent were classed as well developed. Many of these were apparently hypertrophied, although no definite comparison was made with the normal. The general impression is, however, that the superior constrictor muscle elements are better developed in cleft than in normal palates.

The fact that all repaired cleft palates are as a rule shorter and less mobile than normal palates and yet adequate closure is obtained frequently tends to suggest the importance of this hypertrophy of the superior constrictor muscle for speech.

Importance of the Uvula.—Sixty-one per cent of the patients having long uvulas had some nasalization; 55 per cent of those with median length uvulas were thus affected; 71 per cent of those with short uvulas had nasalization; 78 per cent of those with no uvula were thus afflicted, and 56 per cent of those with bifid uvulas had nasalization.

As there is little consistency in these results, this would tend to show that the uvula is of negligible importance in closure of the velopharyngeal sphincter.

Effect of Adenoidectomy and Tonsillectomy.—That adenoidectomy and tonsillectomy considerably enhance the ability to speak well has often been noted.

One patient (in case 6) was observed before adenoidectomy and tonsillectomy and was seen subsequently one week and again one month postoperatively, and a report from the mother was received three months after operation.

Before operation the result had been classed as excellent. There was no phonetic defect, and the palate had a motility of 3 degrees and was of median length. One week postoperatively the motility and length of the palate were the same, but nasalization of 2 degrees was present. The articulation of the consonants was still good, but the nasalization had changed the quality of the speech markedly. The result of the functional test was poor. One month after operation there was less nasalization (1 degree), less difficulty with the functional test was found and the quality of the voice was improving. Three months after operation, the mother reported "steady improvement" in the speech.

It is impossible to draw conclusions from one case, but it seems reasonable to concede that if a mobile palate of good length is present, tonsillectomy and adenoidectomy can be performed without danger of permanent damage to speech. One feels, however, that if the palate is inadequate as to length and motility in the first place, adenoidectomy or tonsillectomy should not be performed.

Value of Speech Training. Fifty-six per cent of the patients in this series have had no speech training. Twenty per cent have had only occasional corrections by the family. Six per cent have had more persistent corrections by the family. Eight per cent have had occasional lessons in speech. Fourteen per cent have had persistent teaching by well trained teachers.

Fifty one per cent of the fifty six who had had no training were classed as excellent as regards their speech, while 28 per cent had good speech, 20 per cent had fair speech and not one had bad speech.

At the other extreme, only 36 per cent of the fourteen who had had adequate training had excellent speech, 57 per cent had good speech, 7 per cent had fair and none had bad speech.

At first glance, these results would condemn speech training as useless, but a study of the anatomic structures of the two groups brings out the fact that a greater percentage of the patients who have had no training have good anatomic structures, whereas in the group which has had training there is a greater percentage of anatomic defects. Moreover, as a rule, only the patients with the poorest functional results have been referred for speech training.

There have been several patients who had had speech training, and although they still have a marked degree of nasalization the articulation of the consonants at the stop position is excellent.

Speech training is most important in perfecting correct articulation. It also assists in developing closure of the velopharyngeal sphincter, but with inadequate anatomic material it cannot possibly do this.

Ultimate Speech Result.—Of the one hundred cases presented, the ultimate speech in 42 per cent was classed as excellent, in 43 per cent as good, in 14 per cent as fair and in 1 per cent as bad or unintelligible.

CONCLUSIONS

1. Good anatomic results do not necessarily mean good functional results.

2. Imperfect closure of the velopharyngeal sphincter is by far the most important anatomic element in ultimate speech results.

3. Velopharyngeal insufficiency is the most important factor in the omission, substitution and disarticulation of most of the consonants. The slurring of s and ch is an exception.

4. Velopharyngeal insufficiency is the cause of the nasalization and therefore the disturbed quality of cleft palate speech. There is a possibility that scar tissue and taut mucous membrane play a rôle in the poor quality by disturbing the vibratory capacity of the cavities of the upper respiratory passage.

5. Abnormal contour of the teeth causes slurring of s and ch.

6. Holes just posterior to the alveolar process in the anterior part of the hard palate have a tendency to cause omission of the labiodental consonants.

7. Small holes in the hard palate cause no phonetic defect.

8. Large holes in the middle portion of the hard palate tend to cause a "hot food" quality to speech rather than a disturbance of articulation.

9. Holes in the lateral part of the hard palate tend to cause a "hot food" quality to speech.

10. Holes in the soft palate tend to cause omission of the posterior linguopalatal consonants.

11. The motility of a palate appears to be more important than length as regards closure of the velopharyngeal sphincter.

12. The superior constrictor muscle elements are important in closure of the velopharyngeal sphincter and are usually hypertrophied.

13. The uvula may be of importance in closure of the velopharyngeal sphincter, but the analysis does not indicate this.

14. A person with a cleft palate usually has distorted nasal cavities, and occasionally the inferior turbinate bones are enormously dilated.

15. Adenoidectomy and tonsillectomy are indicated if the motility and length of a palate are good.

16. Speech education is of greatest value in correcting articulation.

17. No amount of education will entirely overcome marked velopharyngeal insufficiency, although it is of definite value in lesser degrees of insufficiency.

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PYOGENIC OSTEOMYELITIS OF THE PELVIS

ANALYSIS AND DISCUSSION OF NINETY CASES

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This study demonstrates the essential similarity of pelvic osteomyelitis to the more common osteomyelitic manifestations in the long bones. However, pelvic localization is distinguished by its anatomic situation, as defined by the peculiar developmental configuration of the innominate bone and its relation to the adjacent fascial spaces, viscera and the hip joint. These features anticipate the differential diagnostic problems encountered. It is characteristic of the disease that the primary lesion is overlooked or subordinated to the predominant simulative signs and symptoms or to the more extensive secondary parosteal purulent infiltrations. Therefore, pyogenic osteomyelitis of the pelvis continues to challenge diagnosis and treatment during its earlier, more favorable stages, although it is a relatively common devastating disease.

In a series of 1,496 cases of pyogenic osteomyelitis, there were 90, or 6 per cent, in which the focus of infection was in the pelvis. This lesion was third in the order of relative frequency. The ratio (table 1) of males to females in the group of 90 cases was approximately 2:1, except in the group in which the infection was in the sacro-iliac region. The age range was from 2 to 63 years, with an average age of 16 years. Pelvic osteomyelitis is primarily a disease of the growing period. The majority of cases (about 60 per cent) occurred in the second decade. Because of the relation of the sacro-iliac region to spinal foci, there is a relative increase in the later decades.

PATHOGENESIS (TABLE 2)

The apparent port of bacterial entry could be determined in 20 instances. In 17 it was a topical infection and in 3 an acute infectious disease. Boils were the predominant localized infection of the skin. The relationship between such ports of entry and the osteomyelitic process is not always clearcut. Adequate treatment of all topical focal infections, as well as of acute infectious diseases, is an important prophylactic measure. Antecedent trauma was recorded in 35 cases. In most of these the onset of symptoms followed direct or indirect injury,

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Services of Drs. A. Steindler and H. L. Beye.

sometimes dramatically so. The crests of the ilium are not well protected by the soft parts. The sacro-iliac joints are notoriously prone to indirect strains. The ischium and the pubis are readily injured by falls on the buttocks and especially by straddling. The relationship between antecedent trauma and pelvic osteomyelitis substantiates the time-honored assumption of its etiologic importance.

Pelvic osteomyelitis may be classified as a direct or a hematogenous infection. The former follows gunshot wounds, operations and compound fractures or is due to extension from a neighboring suppurative process and infected decubiti. There were 23 (about 26 per cent) cases of direct infection. In 2 cases sacro-iliac osteomyelitis followed arthrodesis, in 1 it was due to extension from an iliac osteomyelitis and in 7 it was associated so closely with disease of the lumbosacral region as to preclude initial localization. In 4 cases iliac osteomyelitis was due to extension from the initial lesion of the hip, and in 1 it resulted from an infected compound fracture. In the 4 cases of ischiac osteomyelitis the condition originated from primary foci of the hips. In 1 case pubic osteomyelitis occurred after a simple fracture, which was operated on and fixed by wire; in 2 it followed pelvic fracture and was associated with genito-urinary complications, and in the fourth it was due to a dissecting superficial abscess of the groin.

Table 1.—*Sex and Age Incidence in Ninety Cases of Pyogenic Osteomyelitis of the Pelvis*

	Ilium	Sacro-Iliac Joint	Ischium	Pubis	Total
Sex:					
Males	20	22	14	6	62 (68%)
Females	11	7	7	3	28 (32%)
Age, years:					
Youngest	4	5	2	4	3
Oldest	63	50	33	59	51
Average	16	21	11	16	16
Decades:					
1	5	2	9	3	19 (21.11%)
2	21	19	10	3	53 (58.88%)
3	1	1	1	1	4
4	2	1	1	1	5
5	1	5	0	0	6
6	0	1	0	1	2
7	1	0	0	0	1

Sixty-seven (74 per cent) of the cases of pelvic osteomyelitis were of the hematogenous form; the lesions in 55 were initial, and in 12, metastatic after the establishment of a bony focus elsewhere. On the basis of the predilection of pyogenic osteomyelitis for growth zones, a diphasic clinical syndrome may be observed as a general rule, corresponding to the two periods of bony development. The first period extends from infancy to puberty, at the end of which period the three bones composing the acetabulum fuse. The second period commences with the ossification of the acetabulum and the appearance of the marginal epiphyses and extends to the time of fusion of the marginal epiphyses, at about 25 years of age. The first period is characterized by a more diffuse lesion, almost invariably occurring at the border of the acetabulum. The second period localizes about the marginal epiphyses. In the sacro-iliac region the initial process begins most commonly on the sacral side but may originate in the ilium or the joint proper. Very soon, however, the entire joint is involved.

Staphylococcus was recovered in the great majority of instances. Sterile cultures are also significant, since the organism may be in the bone and not free in the exudate. Sterile cultures always indicate a most careful laboratory search to rule out tuberculosis, a malignant process or some unusual bacterial invader. The mixed forms are secondary invaders for the most part. Careful initial blood and local cultural studies reveal not infrequently the presence of several organisms, which are apparently simultaneous primary bacterial invaders. Most frequently there is recovered a combination of staphylococci and streptococci. A positive blood culture yielding staphylococci or streptococci is of considerable differential diagnostic importance.

TABLE 2.—*Pathogenic Classification of Cases of Pelvic Osteomyelitis* *

	Ilium	Sacro-Iliac Joint	Ischium	Pubis	Total
Direct infection	5	10	4	4	23 (25.55%)
Hematogenous infection					
Primary lesion	20	16	15	4	55 (61.11%)
Metastatic lesion	6	3	2	1	12 (13.33%)
Infectious agent					
Staphylococci	12	14	12	4	42
Streptococci	3	2	0	0	5
Mixed infection	2	2	1	0	5
Sterile culture	1	4	0	1	6
Positive blood culture	4	2	4	0	10

* Possible ports of bacterial entry and antecedent trauma play an important rôle in the apparent pathogenesis in this series. The latter was recorded in 35 instances of the disease in the following sites: sacro-iliac joint, 12; ilium, 8; ischium, 11, and pubis, 4. There were 17 recorded instances of previous topical infections, which occurred as follows: sacro-iliac joint, 6; ilium, 5; ischium, 5, and pubis, 1. There were 3 instances of previous acute infectious diseases: sacro-iliac joint, 1, and ilium, 2.

PATHOLOGIC ANATOMY (TABLE 3)

There were 4 cases in which the lesions were bilateral, all of which proved to be fatal; in 3 the sacro-iliac joints and in 1 the ischiums were involved, making a total of 94 foci. The cases of bilateral sacro-iliac osteomyelitis were associated with involvement of the lumbosacral region, and the cases of ischiac osteomyelitis, with extensive hemipelvic disease. Pelvic localizations are all more or less diffuse, owing to the peculiar bony configuration and the tendency to chronicity, especially after obliteration of cartilaginous barriers. Seventy per cent were associated with other segmental foci, chiefly by extension. The hip joint is the most frequent site of an associated focus.

The most striking pathologic feature of pelvic osteomyelitis is the relatively "dry" bony reaction as a subacute or chronic fibrous type of osteomyelitis. Conversely, extensive suppuration of the soft tissue is characteristic. The fibrous reaction is partly due to collateral ischemia. The initial site of involvement usually reveals a more active inflammatory reaction. Sequestration is not as uncommon as the literature would indicate. The preponderance of cancellous bone, negligible marrow cavity and excellent circulation is inducive to caries rather than to necrosis. In the sacro-iliac region sequestrums are small and usually situated antero-inferiorly. The changes in the joints are the same as those of infectious arthritis elsewhere. The thin cortical bone of the iliac wing leads to early perforation and variable-sized sequestrums, especially on its pelvic surface. Consequently, it is common to observe at operation the formation of large irregular cisterns on the pelvic surface of the bone, which are filled with pus, sequestrums and débris (fig. 12). Occasionally the entire wing is converted into a variegated necrotic mass. At operation in the later stages of the disease the ischium lies in a soggy bed and can be lifted out *en masse*.

TABLE 3.—*Pathologic Anatomy in Cases of Pelvic Osteomyelitis*

	Ilium	Sacro-Iliac Joint	Ischium	Pubis	Total
Unilateral osteomyelitis	31	26	20	9	86
Bilateral osteomyelitis	0	3	1	0	4
Extensive lesion	17	20	13	3	53 (58.88%)
Localized lesion	14	9	8	6	37 (41.12%)
Associated extension					
Pelvic lesions					
Hip	13	5	7	1	26 (44%)
Ilium	..	7	3	..	10
Ischium	3	..	..	1	4
Pubis	1	..	4	..	5
Lumbosacral portion of spine	..	8	..	..	8
Sacro-iliac joint	6	..	..	..	6
	23	20	14	2	59 (70%)

A striking feature of the later stages is the amount and irregularity of new bone formation. The periosteum is very active in cases of pelvic osteomyelitis, and the tendency toward regeneration—even after total resection—is almost certain in the young. This regenerative irregularity often adds to the operative difficulties encountered. The power of the periosteum may be weakened or inhibited entirely in older persons or because of constitutional inferiority, initial thrombosis and death of the periosteum or intense parosteal infection. Necrosis and intense edema of the surrounding soft parts may predominate the situation. Even in the early stages the histologic tendency toward thickening and eburnation of the bony lamellae is conspicuous.

COMPLICATIONS (TABLE 4)

The complications of pelvic osteomyelitis especially reflect the clinical life history. The dovetailedness of these phenomena reveal an apparent harmony, imperceptible from any other perspective. It is now evident that most complications are of surgical interest, since the vast majority are dependent on the local skeletal lesion. Table 7 indicates this clearly.

Suppuration was observed in over 83 per cent of this series and largely determined the course of the disease. These abscesses tend to gravitate and accumulate in the anatomically related fascial spaces of the thighs, the lower part of the back and the gluteal regions, which are easily invaded. Such purulent collections predominate the surgical situation not alone because of their complexity and bulk but because their shaggy infiltrated walls become in themselves formidable sources of local and systemic infection.

The possible pathways taken by pus originating in the sacro-iliac joint after it has perforated anteriorly illustrate the ramifying tendencies of all pelvic lesions. Pus may follow along the iliopsoas muscle to the inner aspect of the thigh or along the pectineus muscle posteriorly; it may enter the hip joint via a bursa found between the iliopsoas tendon and the anterior part of the joint, or it may burrow posteriorly along the obturator internus muscle or along the pyriformis muscle as a low gluteal abscess or upward from the iliac fossa into the lumbar region. Abscesses arising from iliac foci are of special interest because of their relation to the inner surface of the bone, which is divided by the iliopectineal line into an upper, expanded, portion and a lower, smaller, part. The iliac fossa above and anterior is smooth by sloping, which explains the great prevalence of abscess formation in this region and its tendency to point anteriorly in Scarpa's triangle; since pus is blocked from passing farther into the true pelvis by the structures attached to the iliopectineal line, gravity forces it forward rather than backward. Infected compound fractures of the pubic bones are especially interesting because of the relationship of the bladder and the posterior portion of the urethra. An extensive abscess in the space of Retzius was observed in 1 case in which the pyogenic infection was associated with traumatic rupture of the posterior portion of the urethra. Suprapubic cystotomy and perineal urethrotomy were performed, and the patient died after a stormy course of three weeks' duration.

CLINICAL ANALYSIS (TABLE 5)

In a general way the onset of the disease determines whether the local or the systemic reaction will dominate the initial clinical stages. The disease becomes chronic in practically all survivors, as shown by the average duration of symptoms in this series. The paucity of recorded clinical dates emphasizes the unsuspected nature of the disease in many of these cases. There are, however, sufficient facts obtained to indicate the general clinical picture. It should also be remembered that rather extensive destructive lesions of a low grade nature may present few or no symptomatic clues. In retrospect, it is evident that a knowledge of the disease is of primary importance for a reasonably early diagnosis.

DIAGNOSIS

The chief differential diagnostic interest centers about the hip joint. However, this also involves a discussion of a wide variety of other extrapelvic lesions, such as inflammation of the lower part of the abdomen and pelvis, spondylitis of the lumbar and lower part of the dorsal region, subgluteal bursitis, ischiorectal abscess, isolated abscess of the iliopsoas muscle and bursitis, as well as malignant lesions and tuberculosis. Ruling out actual involvement of the hip joint offers the greatest clinical obstacle to a reasonably early diagnosis, since a sympathetic juxta-articular effusion occurs so frequently. It should be remembered

TABLE 4.—*Complications in Cases of Pelvic Osteomyelitis*

	Ilium	Sacro-Iliac Joint	Ischium	Pubis	Total
Suppuration	27	21	18	9	75 (83.33%)
Pelvic	15	10	2	1	28 (37.33%)
External	7	4	11	3	25 (33.33%)
Thigh	5	7	5	5	22 (29.44%)
Flare-up	13	17	7	3	40 (44.44%)
General sepsis	12	15	5	5	37 (41.11%)
Spontaneous sinus	9	11	7	2	29 (32.22%)
Deformity	15	4	6	1	26 (28.88%)
Skeletal metastasis	9	6	7	1	23 (25.55%)
Sequestrum formation	11	4	4	2	21 (23.33%)
Vascular complications	2	2	..	..	4
Decubiti	1	2	..	..	3
Amyloidosis	..	2	..	..	2
Rectal perforation	1	..	1	..	2
Peritonitis	1	..	..	..	1

TABLE 5.—*Clinical Analysis of Cases of Pelvic Osteomyelitis*

	Ilium	Sacro-Iliac Joint	Ischium	Pubis	Total
Onset					
Acute	13	11	9	5	38
Subacute	7	7	5	4	23
Chronic	6	3	2	..	11
Duration, months					
Shortest	0.15	0.3	0.1	0.1	0.16
Longest	676	84	276	132	202
Average	47	27	34	35	33
Symptoms					
Subjective					
Pain localized	7	10	4	4	25
Pain referred	9	10	6	2	27
Objective					
Local tenderness	8	10	10	3	31
Muscle spasm	3	3	..	1	7
Loss of weight	9	8	3	4	24
Superficial abscess	8	3	6	3	20
Pelvic abscess	5	6	..	..	11
Edema and infiltration	5	6	6	2	19
Deformity of hip	10	13	7	1	31

in this connection that the joint may be the primary seat of infection, be affected simultaneously or included in the process by extension secondarily. Marked symptoms referable to the hip joint, especially when accompanied by radiating pain along the internal obturator nerve, are almost pathognomonic of relative or absolute participation of the hip joint in the disease.

Primary disease of the hip joint is early associated with more or less of a position of instability of the joint, mainly flexion, abduction and external rotation. The flexed position may be combined with adduction and internal rotation. This position is conditional on the relationship of the initial localization of the infection to the anatomic quadrants of the acetabulum, the head of the femur or the pelvifemoral musculature. Thus the resultant subsequent position of the hip is maintained by a specifically activated protective muscle spasm pattern characterized by relative or absolute spasm. However, some degree of motion may be elicited before the joint cartilage is involved, or in the more chronic lesion due to the capsular and ligamentous relaxation incident to a prolonged state of hydro-arthrotic distention. When the disease is in the pelvis, the attitude of the hip and the limitations of joint motion are less significant. Extra-articular conditions will allow a considerable range of motion in the joint in the planes not controlled by those pelvifemoral muscles arising or inserting at sites of bony involvement. Therefore, the attitude of the hip is now sympathetic and relatively atypical. When the focus is in the ilium, the hip is characteristically in flexion and abduction. Flexion predominates when the focus is in the sacro-iliac joint. When the infection is localized in the ischium, external rotation of the femur is present. If the disease is in the pubis, there follow flexion, adduction and internal rotation as a rule.

Aspiration of the hip joint and surrounding structures is the most important single factor in the clinical evaluation of suppurative localizations. This must be persisted in intelligently and may be performed with the patient under general anesthesia. The gross and laboratory examinations of the material withdrawn yield the key to the situation.

Special emphasis should be given to the infection in the sacro-iliac region, since it involves the syndrome of pain low in the back. It may be impossible to make a differential etiologic diagnosis without exploration and biopsy. Even so, the laboratory tests were misleading in several cases in that the exudate yielded a positive reaction when injected into a guinea-pig, but the reaction was not substantiated by subsequent autopsy examination or pathologic studies of sufficient material removed at operation. Disease of the sacro-iliac joint often simulates disease of the hip joint. On examination the motions of the hip will be free, except the extremes of flexion and extension, because the former puts tension on the hamstring muscles, which is transmitted to the sacro-iliac joint, and in sacro-iliac involvement the latter is restricted by associated spasms of the iliopsoas muscle. It is most difficult to differentiate sacro-iliac osteomyelitis from sacro-iliac tuberculosis. Ombredanne considered the latter to be rare in infancy, and Wilmath stated that it is exceptional before the age of 20. In children the tuberculous process of the os ilium originates at some distance from the bone as osteomyelitis. It is more rapid in the adult and is primarily an involvement of the joint or osteo-arthritis. The initial reaction may, however, be ushered in by a septic fever or the appearance of a tuberculous focus in other places. In the adult type of sacro-iliac tuberculosis in the early stages there are five symptoms of value: sacroradiculitis, painful limp, sacro-iliac diastasis (noted roentgenographically) and upward displacement of the pubic bone and, finally, localized surface and rectal tenderness, elicited digitally.

Abdominal and pelvic inflammations are simulated chiefly by localizations of the disease in the sacro-iliac joint and in the ilium, especially in the latter. In the acute stages the profound general reaction and bacteremia point toward pyogenic skeletal disease. Careful observation of spontaneous and of provoked pain is a great aid in the diagnosis. Spasm of the abdominal muscles, when present, confines itself to the iliac crest and soon takes on the character of induration and even of edema. This tenderness even very early may be outlined in the posterior portion of the ilium along the crest or even may simulate a perinephritic abscess. Tenderness is common in the groin but cannot be accurately limited. When perforation occurs, the temperature and the general condition are improved. Some pain persists, however, and soon a purulent collection in the pelvis is clinically evident. In acute pubic lesions one has to distinguish between phlegmonous inflammation in the space of Retzius, suppurative arthritis, psoasitis and myositis of the rectus abdominalis muscle. Ischiac lesions offer no particular difficulties if the examiner thinks of the possibility.

ROENTGENOGRAPHIC EXAMINATION

The roentgenogram is indispensable for diagnosis and proper surgical evaluation, particularly in the subacute and chronic stages of the disease. The entire pelvis and the lumbar portion of the spine must be carefully checked after the patient has been properly prepared. Several pronounced lesions of the iliac wing were missed early in the series because of failure to observe this simple detail. Lateral views of the iliac bones and hips are helpful, since localized lesions of the ilium can be visualized even early. Although the general operative risk determines the surgical indication, no operative procedure can be intelligently planned without a complete preliminary roentgenographic study of the situation. The changes in the soft tissues are of some significance in the early stages of acute inflammatory conditions and are observed as capsular and other fascial and muscular distortions and infiltrations. In cases of ischiac lesions the obturator foramen may be clouded early because of abscess formation. The hip joints must be extended if possible to avoid superimposed shadows from the tissues of the thighs. The essential changes depicted by the roentgenogram are osteoporosis, sequestration and bone production. Osteoporosis is the earliest sign in the acute stage. Its delay is due to the fact that the calcium salts early remain at the site of involvement in an attempt to limit the pathologic process. It appears soonest in the more primitive cancellous portions of the bones in which calcium is not so bound up as in the more highly organized haversian architecture prevalent in cortical bone. Because osteoporotic changes sometimes persist, these lesions simulate tuberculosis and even malignant processes. Except in the pubis and the sacro-iliac region, the regenerative features are characterized by great thickening and irregularity. In the chronic phases there is left a mass of irregular sclerotic thickened periosteal bone with little or no architectural detail that can be made out. The value of injection of a sinus with a radiopaque substance cannot be overemphasized as an aid to diagnosis.

END-RESULTS (TABLES 6 AND 7)

The inadequacy of treatment previous to hospitalization reflects the general attitude of the medical profession toward this disease. These lesions have always been considered as hopeless and attended by a grave prognosis. Of the 29 cases of sacro-iliac lesions, the superficial abscess was incised in 7 and aspirated in 2. Of the 21 cases of ischiac osteomyelitis, incision was performed in 5 and curettement in 1. Of the 21 cases of iliac lesions, curettement was performed in 4 and simple incision in 4. The pubic lesions were not treated. The treatment in the hospital also indicates an absence of definite principles in the earlier cases. On the whole, the best results were obtained after the need for more adequate treatment was recognized.

Of the 18 cases of sacro-iliac osteomyelitis in which the bone was attacked, curettement was done posteriorly in 5, and the Smith-Petersen technic was used in 5, total resection in 3 and partial resection in 5 (1 bilaterally). The Smith-Petersen technic is adequate for circumscribed lesions, especially when reenforced by Orr's postoperative routine. In 1 case this procedure was followed by total resection at a later date. In the second case two further operations were necessary. In 2 the lesions were not suppurative, and in the fifth a subgluteal abscess developed one month after operation. In 7 cases simple incision and drainage were employed, the only favorable result being obtained by the Orr method. There was no operative mortality in the group in which resection was done. Three patients died subsequently from complications already present at the time of operation. In 5 cases healing occurred in from six months to one year.

In the group of patients with iliac osteomyelitis there were 2 adolescents (1918 and 1927) who were treated by roentgen irradiation, with apparent cessation of the clinical symptoms. Five of the patients were not treated for one reason or another. Three were treated by sequestrectomy without success. Thirteen were treated by simple incision and drainage; healing occurred in 1, and 3 died. Of the more radical procedures, total resection was performed once, partial resection four times, saucerations several times and trephination once. In the case in which trephination was done over 50 metastatic foci subsequently developed. There was only 1 death in this group.

TABLE 6.—*Treatment and End-Results in Cases of Pelvic Osteomyelitis**

Type of Treatment	End-Result	Ilium	Sacro-Iliac Region	Ischium	Pubis	Total
Radical................	Healed	7	13	4	2	26
	Died	1	3	2	1	7
	Unknown	2	2	2	0	6
Incision................	Healed	1	1	2	1	5
	Died	3	1	1	0	5
	Unknown	9	3	3	3	18
Conservative...........	Healed	4	1	0	0	5
	Died	0	0	1	1	2
	Unknown	4	5	6	1	16

* This table classifies the treatment as a whole. Radical treatment indicates that the affected bone was attacked in one way or another. The affected bone was not attacked at all in the cases included under simple incision. Conservative treatment includes roentgen irradiation, the use of casts or other mechanical methods, simple hospitalization or no active treatment at all. The mortality as regards the cases as a whole is: radical treatment, 18 per cent; incision, 18 per cent, and conservative treatment, 9 per cent. However, on the basis of the cases in which the end-results were known the mortality is as follows: radical treatment, 21 per cent; incision, 50 per cent, and conservative treatment, 40 per cent.

TABLE 7.—*End-Results in Unselected Cases of Pelvic Osteomyelitis in which Resection Was Performed*

Localization	Operation	Number of Cases	Healed	Died	Mortality
Sacro-iliac joint.........	Partial resection	5	3	2	40%
	Total resection	3	2	1	33.33%
Ilium....................	Partial resection	4	3	1	25%
	Total resection	1	1	0	0
Ischium.................	Total resection	4	4	0	0
		17	13 (76.48%)	4	23.52%

Simple incision and drainage were performed in 6 cases of ischiac osteomyelitis, with cures from well circumscribed foci in 2. The disease was bilateral in 1 of the remaining 4 cases, and it extended to the hip in 1 and to the ilium in the other. In the fourth case the condition proved fatal. Death also occurred in the 2 cases in which sequestrectomy was performed and in 1 case in which a simple incision was done. In another case a mistaken diagnosis of disease of the hip joint was made, and operation was performed, with fatal results. The radical operations (resection) were performed in the acute and subacute stages of the disease with sound healing within from three to six months.

In the 5 cases of direct infection of the pubic bone, simple incision and drainage were employed. Autopsy in the fatal cases revealed a huge abscess in the space of Retzius, which extended laterally into the iliac fossae. The metastatic focus in the cases of hematogenous infection drained spontaneously. Sequestrectomy was performed on a boy two weeks after onset, with healing in four months. Simple incision on a 4 year old girl, three weeks after an acute onset, ended in extension of the lesion and death. A youth aged 17 years was treated by a cast, with subsequent invasion of the anterior compartment of the thigh. The most gratifying and convincing result followed prompt adequate treatment in a case of acute involvement in which the abscess and involved bone were treated by the Orr method.

TREATMENT

The need for radical treatment was recognized and urged by the earliest writers on iliac lesions. Perhaps their very zeal delayed the acceptance of these principles. An extended experience with pyogenic osteomyelitis supports this fundamental therapeutic truth relative to established foci of the disease. One should remember that the lesion may be nonsuppurative and that spontaneous healing may occur. However, pelvic osteomyelitis is essentially a most devastating disease which demands bold operative measures. The key to the individual situation is revealed by the complications of the disease in general. The vast majority of these depend primarily on the skeletal lesion and only secondarily on any existing systemic reaction. Therapy now resolves itself into the primary and secondary control of the disease.

Primary control of the disease involves the initial systemic infection and the determination of the local suppurative focus. These must be considered in the order of their appearance. Henceforth the most aggressive measures continue to be directed against whichever predominates the clinical situation. Until contradictory knowledge affecting the relationship between the port of bacterial entry, the systemic infection and the local lesion is attained, adequate drainage is indicated when localization is clinically established. Pyogenic osteomyelitis anywhere is not a surgical problem until this occurs. The successful termination of the acute stages of the disease depends on the surgeon's experience with the disease. Therefore, treatment at the onset must be directed against the systemic situation by the several means at one's command —dextrose solution intravenously, small repeated transfusions, sedatives, splinting, traction or casts—and one should ever be on the watch for localizing skeletal signs and symptoms. Perhaps early diagnosis and immediate bony drainage have been overemphasized at the expense of a careful evaluation of the surgical risk. The fault rests with the individual surgeon. Poor preoperative surgical judgment reflects unfairly on and discredits sound axiomatic principles of drainage. However, the conservative postoperative technic of Orr permits more extensive surgical treatment in the early stages than would otherwise be feasible in pelvic localizations of the disease.

As a rule the signs of localization in the soft tissue appear within a few days of the onset of symptoms. Simple incision and drainage will suffice until more definite pathologic skeletal delineation is manifest. By this time the operative risk and the operability of the lesion will determine all further operative details. Wide excision of affected bone is the ideal to be attained. Several factors are effective indicators of improvement of the patient's operative risk and of definite establishment of localization of the disease: a decrease in the initial rapidity of the sedimentation rate, intermittent fever after an initially sustained level of temperature, associated with a lowered pulse rate, a fair cellular blood level and even diminished apprehensiveness and pain.

Secondary control of the disease is based on anticipation of pathologic extension, sequestrum, secondary infection, persistent sinus and flare-ups and above all on locomotor disturbances. The patient now definitely becomes a veritable battleground between the conscientious surgeon and complications, which are practically all preventable or amenable to treatment. Extension of the disease involves chiefly the adjacent joint or joints and the fascial spaces and their contents. Sinus formation enhances secondary infection or even malignant change. Locomotor disturbances are caused principally by deformities of mechanical origin. All of these can also be most uniformly prevented by observing Orr's second great principle, that of adequate rest of the parts.

Pelvic osteomyelitis adapts itself to radical treatment in spite of the apparent complexity of the anatomic situation. The peculiar anatomic structure of the bony pelvis permits a diffusion of functional stresses for its weight-transmitting function through its posterior and anterior arches. The complexity of the soft tissue elements of the pelvis is compensated for by the ready subperiosteal surgical exposure of the bony segments.

The irregular structure of the innominate bone is dissipated when it is regarded as a figure 8 twisted on itself. The acetabulum is therefore situated at the isthmus. The upper two-fifths forms the ilium; the ischium comprises the lower and posterior two-fifths, and the pubis, the remaining one-fifth. The fairly even distribution of the parts is not generally appreciated. The thicker parts of the iliac bone consist of cancellous tissue enclosed within two layers of compact tissue, which are lined by periosteum. The thinner parts of the bottom of the acetabulum and the center of the iliac fossa are transparently thin and composed entirely of compact tissue. The inner surface of the ilium is of interest in relation to pyogenic infection. In general, the ischium is the posterior and inferior portions of the lower expanded part of the innominate bone and helps to form the posterior boundary of the obturator foramen. The body is the lower two fifths of the acetabulum and spine of the ischium and is limited below by its neck. The posterior border of the neck is the lesser sacrosciatic notch. The tuberosity of the ischium continues down from the neck to the ascending ramus and forms the rocker of a rocking.chair. It is triangular in cross-section. The ascending ramus is a thin plate of bone going up to meet the descending ramus of the pubis. These two pubic bones complete the pelvic girdle and consist of a body and a descending and an ascending ramus. The descending ramus meets the ischium and completes the boundary of the obturator foramen. The ascending ramus goes laterally from the body and upward to end in the acetabulum. The body is the portion at the symphysis and has a quadrilateral form. Its upper border is thicker than the lower.

The sacro-iliac joint is a true joint cavity and has a synovial lining, which is supported by a capsule. The joint surfaces are ordinarily smooth, save for sufficient roughening to lock the joint surfaces. The lumbosacral cord lies directly over the lower third of the sacro-iliac joint. In this region nothing except the joint capsule intervenes between the nerve trunk and the joint space. The proximity of the superior gluteal vessel to the inferior margin of the greater sciatic notch offers a real danger during resection of the sacro-iliac joint and ilium. Enormous superior gluteal arteries, often the size of a man's thumb, have been found in cadavers. The vessels are separated from the ilium only by the periosteum. They are about 1 inch (2.5 cm.) long and have a tendency to retract into the pelvis when severed. Other structures in close proximity to the anterior portion of the sacro-iliac joint in the pelvis that are of surgical importance are the great pelvic vessels, the ureters, the lumbosacral plexus and the rectum. The rectum forms at the third sacral segment and accommodates itself to the hollow of the sacrum and the coccyx. All of these are more or less protected by the iliopsoas structures, which are further thickened by inflammatory edema and infiltration when the sacro-iliac joint is involved by osteomyelitis.

The sacro-iliac joint and adjacent structures are attacked by the Bardenheuer-Picque technic.

In resection of the ilium a Smith-Petersen incision permits the entire external soft tissue flap to be stripped down to the margin of the acetabulum and is followed by anterior deep dissection to expose the anterior portion of the ilium. Posteriorly, the exposure continues to the greater sciatic notch. Next a similar subperiosteal exposure is made of the internal surface of the ilium. At this stage it is remarkable to note how the abdominal contents fall away to complete the exposure of the wing of the ilium down to the arcuate line of the ilium. In cases of chronic involvement subperiosteal dissection will be somewhat difficult because of scarring due to perforation and the formation of an involucrum. One may then remove the ilium as indicated or *en masse* to the supracotyloid region.

My technic for resection of the ischium employs a posterior vertical or transverse gluteal approach, because it is adequate, is farther from the anal canal, furnishes a thick soft tissue pad for subsequent healing and does not require any unusual position of the patient. An incision of from 4 to 6 inches (10 to 15 cm.) long is made over the lateral margin of the tuberosity of the ischium. The dissection continues to the tuberosity. The lowermost fibers of the gluteus maximus fibers are encountered and may be retracted upward or incised near their lower origin. Next the sciatic nerve is located lateral to the tuberosity, freed and retracted lateralward and slightly upward with the fibers of the gluteus muscle. The periosteum and ligamentous attachments of the tuberosity are now boldly incised to the bone between the medial and the lateral hamstring muscles and the external rotator muscles of the hip. Subperiosteal stripping continues upward and downward as far as is necessary to remove all the involved bone. One can proceed to the acetabulum or to the pubis. The stripping is enhanced because of the thickening and edema of the periosteum usually present in osteomyelitic foci. No important structures are jeopardized if the dissection is continued strictly to the subperiosteal region, as these are all lifted away medially and laterally with the basic periosteal flaps. The bone can be removed piecemeal with the curet or rongeur or severed with a saw or mallet and chisel. In extensive lesions the entire bone may be lifted out of its bed. With ordinary care in sealing off the wound, rectal contamination does not occur. The patient may be constipated for several days after operation by the administration of opium.

REPORT OF CASES

Osteomyelitis of the Sacro-Iliac Joint.—CASE 1.—L. B., a white boy aged 15 years, was admitted to the hospital on Dec. 16, 1931, with symptoms of six weeks' duration. The condition began suddenly, with headache, chills, fever and a dull aching, nonradiating pain "back of the right hip," soon accompanied by diarrhea and urinary frequency. Objectively, there was fulness in the right lower abdominal quadrant. Moderate swelling and tenderness were noted over the right sacro-iliac region. Digital rectal examination revealed a tender fluctuating mass at the lower margin of the right sacro-iliac joint. The white cell count was 14,200. Roentgen examination confirmed the destructive nature of the sacro-iliac and the adjacent iliac lesion (fig. 1). A diagnosis of pyogenic osteomyelitis was made.

Operation.—Total resection of the sacro-iliac joint was done in January 1932. The periosteum of the ileum was found to be thickened, gelatinous and of a dirty grayish color. The bone beneath was injected and roughened. At the junction of the middle and the posterior third of the ilium, just below the crest on the pelvic surface, there was encountered a sequestrum measuring about 3 inches (7.6 cm.) in diameter. It lay loosely in a subperiosteal crater of pus and débris. Thick pus was present in the anterior part of the joint as well as another sequestrum. Most of the sacrum was necrotic, and considerable curettage was necessary to reach healthy bone. The immediate postoperative convalescence was uneventful.

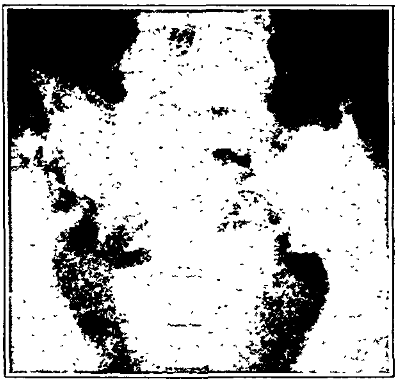

Fig. 1 (case 1.)—Roentgenogram showing sacro-iliac osteomyelitis with sequestrums in the anterior margin of the joint and the posterior wing of the ilium. There is slight asymmetry of the pelvis.

The temperature was normal two weeks after operation. Staphylococcus aureus was recovered. The diagnosis in the pathologic report was pyogenic osteomyelitis. Complete healing occurred in about eighteen months.

Case 2.—R. C., a white man aged 21, was admitted to the hospital on Sept. 23, 1931, with symptoms of ten days' duration, which were of sudden onset, with a dull aching pain in the left groin, painful micturition and fever. The patient appeared acutely ill and septic. The left inguinal glands were enlarged and tender. A tender soft mass could be palpated in the lower part of the left side of the pelvis. There was suggestive tenderness over the left sacro-iliac region. A roentgenogram revealed blurring and increased condensation about the sacro-iliac joint. The white cell count was 16,500. General hygienic measures and traction were continued for several weeks until the diagnosis of pyogenic osteomyelitis was more certain and the operative risk less.

Operation.—Partial resection was done. The sacral portion was markedly necrotic. About 500 cc. of pus was evacuated from the pelvis. There was a moderate degree of shock. Staph. aureus was recovered, and inoculation of a guinea-pig gave negative results. The diagnosis in the pathologic report was pyogenic osteomyelitis. The convalescence was uneventful, except for several metastatic abscesses in the soft tissue. Healing occurred in ten months (fig. 2 *B*).

Case 3.—D. T., a white youth aged 17, was admitted to the hospital on Jan. 18, 1933, with symptoms of four months' duration, consisting of pain in the back and sciatica of acute onset. He had lost 28 pounds (12.7 Kg.) in weight. Two weeks before operation a spontaneous sinus appeared over the left buttock. There was bilateral spasm of the lumbar muscles, which, however, permitted considerable spinal motion. There was definite tenderness over the left sacro-iliac joint. The motions of the hip were free. The white cell count was 11,400. A roentgenogram showed a destructive lesion of the left sacro-iliac joint. A diagnosis of pyogenic osteomyelitis was made.

Operation.—Total resection was done. The chief destruction was found in the upper and anterior poles of the joint, involving the sacrum considerably. The ilium just above the sciatic notch was brittle. Only a few cubic centimeters of pus was encountered in the joint. The patient's recovery was uneventful. Four months later the sinus was again explored, and a small sequestrum was removed. Healing occurred in about one year. No bacterial organisms were recovered at operation. The diagnosis on the basis of the pathologic picture was chronic pyogenic osteomyelitis, with calcification of the joint surfaces.

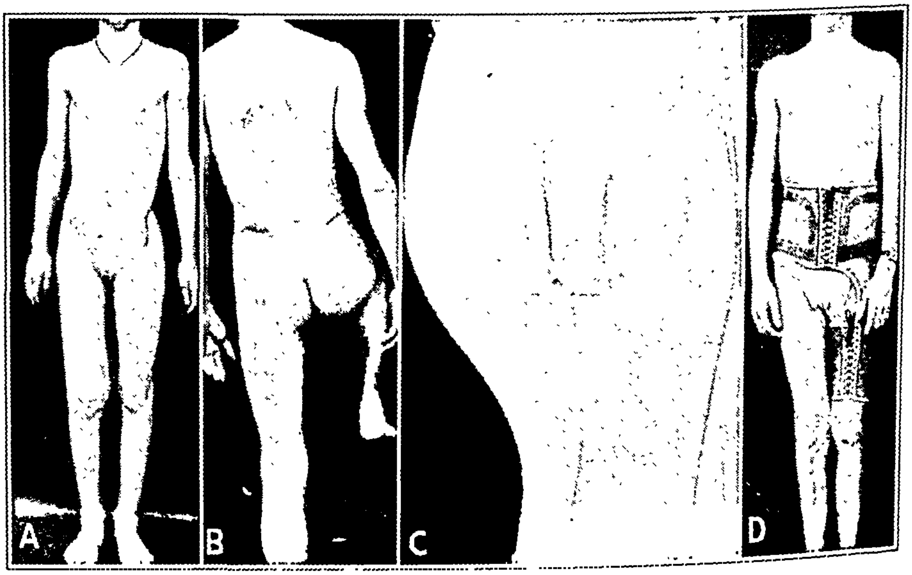

Fig. 2.—Photographs of patients in whom healing has occurred. *A* (case 10) shows a patient with healed osteomyelitis of the ilium; *B* (case 2), a patient with healed osteomyelitis of the sacro-iliac joint, demonstrating a negative reaction to the Trendelenburg test; *C* (case 15), a patient with healed osteomyelitis of the ischium, and *D*, a patient wearing the convalescent brace used for all pelvic foci.

Case 4.—William S., white, aged 38, was admitted on Feb. 14, 1933, with symptoms of two and one-half years' duration. He had definite tenderness over the left sacro-iliac joint and a sinus just above the middle crest of the ilium. In January 1931 he was operated on by the Smith-Petersen method. The operative wound healed in four months after a stormy convalescence, but the original sinus never healed, nor was the patient relieved of his sciatica. A diagnosis of pyogenic osteomyelitis was made.

Operation.—Partial resection was done. The spines of the ilium were roughened and almost fused to the sacrum. The entire joint was destroyed, and the ilium was sclerotic and very thick. The sacral portion was necrotic at the level of the third segment, and the sacral canal was opened in eradicating this area. Blunt dissection of the soft parts of the pelvis led to an abscess. Several branches of the superior gluteal vein were accidentally torn but fortunately could be clamped and ligated. A moderate degree of shock followed. Staph. aureus and streptococci were recovered. The diagnosis on the basis of the pathologic picture was pyogenic osteomyelitis, with secondary productive changes in the joint. The postoperative convalescence was uneventful except for some intrapelvic hemorrhage. Several small transfusions of blood were given, followed by marked improvement in the general condition, and healing was sound in about six months.

CASE 5.—Earnest B., aged 48, was admitted to the hospital in June 1933, with symptoms of four months' duration. The insidious onset was described as a "bellyache." An abscess soon appeared posteriorly. The patient lost some weight and could not bear weight because of pain in the right hip. Fourteen small sequestrums extruded spontaneously. There was a slight scoliosis to the left and a small sinus over the right sacro-iliac region. The skin about this was dull red and edematous. Infiltration and marked tenderness were elicited in this region. A roentgenogram showed an extensive destruction of the entire sacro-iliac joint. A diagnosis of pyogenic osteomyelitis was made.

Operation.—Total resection was done. The iliac flap was rapidly removed with the aid of a motor saw. There was brisk hemorrhage from the smaller vessels. The entire joint was necrotic, but no free pus was encountered. The diagnosis on the basis of the pathologic picture was pyogenic osteomyelitis, with no signs of specific inflammation. There was moderate shock, and the wound did not do so well as was expected. The drainage was profuse. The patient died at home about four months after operation, from an unknown cause.

CASE 6.—Francis H., white, aged 20, had "silent" involvement of the left sacro-iliac joint of about six years' duration. He had multiple foci, including acute spondylitis, all of which necessitated drainage. The sacro-iliac joint was explored as a possible source of continued occasional metastatic foci and was considered to be the initial primary focus. A diagnosis of pyogenic osteomyelitis was made.

Operation.—Partial resection of the sacro-iliac joint was done in September 1933. The joint was found to be fused and obliterated for the most part. The posterior portion of the sacrum was friable. The ilium was dense and sclerotic. The pathologic process consisted of mild subacute nonspecific inflammatory changes. Healing occurred promptly.

CASE 7.—Charles G., white, aged 17 years, had symptoms of one year's duration. There was chronic involvement of the lumbosacral and both sacro-iliac joints. The patient was a very poor operative risk as he was emaciated and covered with decubiti. Operation was performed as a last resort. A diagnosis of pyogenic osteomyelitis was made.

Operation.—Bilateral partial resection was done in February 1934. No frank pus was encountered, but considerable necrosis was present. Staphylococci were recovered. The patient died in about three months.

According to the autopsy report the diagnosis was subacute osteomyelitis of the lumbosacral portion of the spine, the sacro-iliac joints and the innominate bones and thrombosis of the right common iliac and left iliac veins.

CASE 8.—Wayne M., white, aged 23, had metastatic involvement of the lumbosacral and both sacro-iliac joints of about eighteen months' duration. He was very septic and ill. Retroperitoneal drainage was established through Petit's triangle, but he grew progressively worse. A diagnosis of pyogenic osteomyelitis was made.

Operation.—Partial resection of the sacro-iliac joint and evacuation of the retroperitoneal abscess were done in August 1932. The patient died one month later, after a stormy period.

According to the autopsy report the diagnosis was chronic suppurative arthritis of both sacro-iliac joints, osteomyelitis of the lumbosacral portion of the spine, abscess of the right psoas muscle, suppurative phlebitis of the left femoral vein, multiple metastatic abscess of the soft tissue, chronic osteomyelitis of the scapula, amyloidosis of the liver and spleen and septicemia.

Osteomyelitis of the Ilium.—CASE 9.—Margaret F., white, aged 12 years, was admitted to the hospital in 1934 with symptoms of three years' duration. After a local injury she complained of intermittent pain and aching in the left hip and the region of the thigh. She had occasional night cries. She soon became acutely ill and feverish and had severe pain in the left hip and the region of the thigh. Incision and drainage of the thigh were soon followed by spontaneous drainage. The patient was a total invalid after the onset of the symptoms. Examination revealed a sinus in the upper anterior one third of the left thigh. Acute pain was elicited in this region on digital pressure. The hip was fixed in flexion and adduction of 75 degrees, associated with flexion contracture of the left knee of 75 degrees. The general condition was fair. The sedimentation rate was not rapid. The white cell count was 21,300, and the red cell count was 3,400,000. The roentgenogram showed destruction of the entire wing of the left ilium. A diagnosis of pyogenic osteomyelitis was made (fig. 3 *C* and *D*).

Operation.—Total resection was done in March 1934. The approach was difficult because of the contracture of the hip. The sinus led to the true pelvis just over the ascending ramus of the pubis, and pus was encountered when this depth was reached. Three major areas of destruction were found in the ilium (fig. 4). All the periosteal and soft structures were dense and adherent. After complete débridement a fairly dry field remained. Staphylococci were recovered, and the pathologic picture was that of pyogenic osteomyelitis. The most extensive change histologically was an irregular reactive osteosclerotic inflammatory process. The bone marrow consisted of hyperemic fibrous tissue which still showed some cellular infiltration. Destructive activity was only moderate, even in the region of the gross crater abscess, which was covered by scar, on the surface of which the granulations were necrotic. Numerous purulent foci were still present in the more superficial marrow spaces and in the neighborhood of the periosteal abscess, which contained necrotic spicules and was otherwise in an advenced stage of organization. A diagnosis of chronic osteomyelitis with extensive osteosclerosis surrounding periosteal abscess formation was made. The patient had a rather stormy convalescence, but healing occurred in about one year, with little or no regeneration of the iliac wing.

CASE 10.—Gertrude G., white, aged 13 years, was admitted to the hospital in August 1933, with symptoms of two months' duration. The onset and course were subacute. The patient was fairly well nourished and walked with a limp on the left side. The left buttock was flat, and the left trochanter was less prominent than the right. A tender mass was palpated above the left hip joint, which exhibited limitation on rotation. The roentgenogram showed a destructive lesion of the iliac wing simulating tumor formation (fig. 3 *A* and *B*). A diagnosis of tumor or pyogenic osteomyelitis was made.

Operation.—Partial resection was done in August 1933. A tremendous amount of odorless edema and necrosis of the soft parts was encountered. The entire anterior two thirds of the upper half of the ilium was gone except for a small outer shell, which was sequestrated. Within the iliac fossa were found many spiculed sequestrums the size of tooth picks in a mass of débris. The pathologic picture was that of subacute and chronic fibrous osteomyelitis. Histologic examination showed a great amount of young cancellous bone with irregular texture. The bony trabeculae were composed of lamellar bone, fibrous bone and even calcified cartilage in the central portion. In part there was an osteoid layer with signs of inflammation. Between the bony trabeculae in several areas larger masses of hyaline cartilage were interposed, and there was continuous transformation of cartilaginous tissue toward fibrous bone tissue, as is commonly the rule in callous formation or in myositis ossificans. The surrounding soft tissues were represented by transverse striated musculature, which showed the highest degree of edematous infiltration. Among the exudate cells, lymphocytes and polymorphonuclear leukocytes were present. A diagnosis was made of nonsuppurative subacute osteomyelitis and productive periostitis with marked inflammatory edema of the surrounding musculature. There was no suggestion of tumor formation.

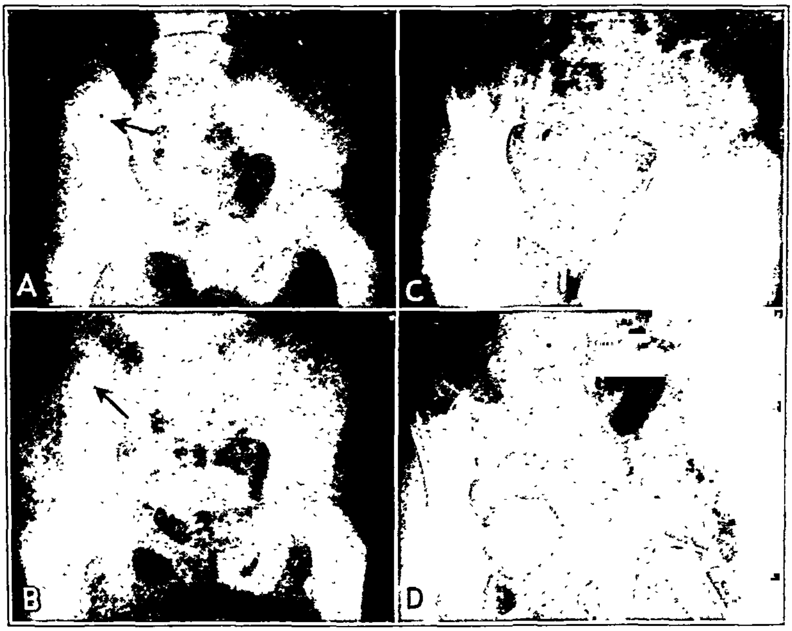

Fig. 3.—Preoperative and postoperative roentgenograms of the pelvis in two cases of iliac osteomyelitis. *A* (case 10) shows an untreated lesion of over two months' duration, which suggests tumor formation rather than inflammation. *B* was made after partial resection. *C* (case 9) shows an untreated lesion of almost four years' duration. *D* was made after total resection. A subtrochanteric fracture was noted after manual correction of the flexion deformity of the hip, performed at the time of operation.

The patient fully recovered in four and one-half months.

Case 11.—Edna H., aged 11 years, was admitted to the hospital on May 13, 1935, with symptoms of ten days' duration. The onset was acute with pain in the right hip and groin associated with high fever, chills and vomiting. The child appeared to be acutely ill. The right hip was held in flexion. Considerable motion of the joint could be elicited, however, when her attention was distracted. The tenderness over the right groin was indefinite. In the right iliac fossa along the iliac crest backward definite tenderness and some muscle spasm were noted. The white cell count was 16,900, and the blood culture yielded staphylococci. In about five days a definite mass formed in the right iliac fossa, simulating an appendical abscess, and the temperature dropped to about 101 F. Serial roentgenograms revealed a supracotyloid destructive process (fig. 5). The diagnosis was pyogenic osteomyelitis as differentiated from acute appendicitis.

Operation.—Partial resection was done. A vertical incision from the iliac crest to the greater trochanter followed by blunt dissection exposed the supracotyloid region. The soft tissues were all edematous, and the outer cortex of the bone was soft and friable. No pus was encountered until the inner table was opened. Staphylococci were recovered, and the pathologic picture was that of acute pyogenic osteomyelitis. The patient continued to have a low grade fever, which subsided only after counterincision and drainage along the iliac crest were performed. Healing occurred in about four months, with a residual ankylosis of the hip joint in good position.

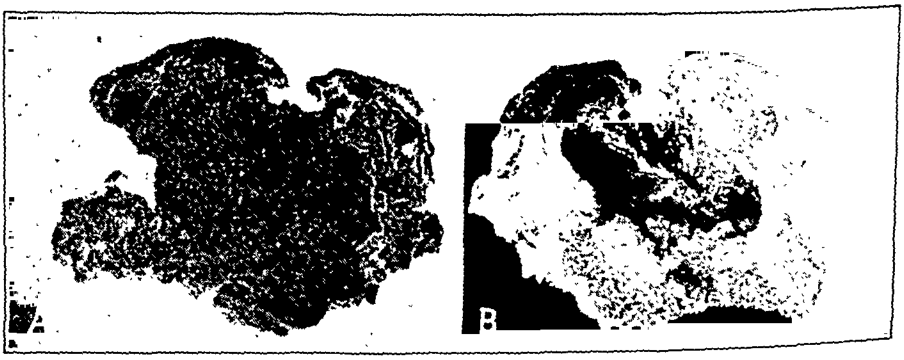

Fig. 4 (case 9).—Pathologic specimens of the iliac wing. *A,* the outer surface. The outer cortex was broken through in two places, one below the anterior superior spine and the second in the middle of the crest, and involved the cartilaginous apophysis as well as the bone. The bone was rather smooth and in many places was covered by densely adherent granulation tissue. The outer cortex formed a shell-like thin layer, whereas the inner cortex, so far as it was preserved, showed considerable thickening. *B,* the inner surface, showing a typical crater defect, with lateral displacement of the outer cortex.

Case 12.—John S., white, aged 41, was admitted to the hospital on Feb. 21, 1936, with symptoms of forty-one years' duration. The present flare-up followed a pathologic fracture of the right humerus. Local symptoms came on acutely with sharp pain about the right hip and flank, and a perirectal abscess presented soon afterward. This was incised and drained. The roentgenograms showed extensive honeycombing and destruction of the iliac wing, hip and trochanteric region (fig. 6). A diagnosis of pyogenic osteomyelitis was made.

Operation.—Partial resection was done on March 31. Numerous sequestrums were encountered. The main pathologic process in the ilium centered about the anterior third of the wing of the ilium. There was a typical crater-like destruction on the pelvic surface, with a considerable collection of débris and pus. A sinus had apparently burrowed downward into the true pelvis. The ilium was tremendously thickened. The hip joint itself was entirely denuded of cartilage and destroyed, but allowed manual correction. There was a moderate degree of postoperative shock. Four days later sepsis developed. The wound, which for one reason or another had been partially closed and inadequately drained, was opened and found filled with purulent exudate. The patient did not rally and died on April 12 of peritonitis, incident to a secondary infection with colon bacilli from the perianal fistula. This was the only case in which the Orr technic was not observed.

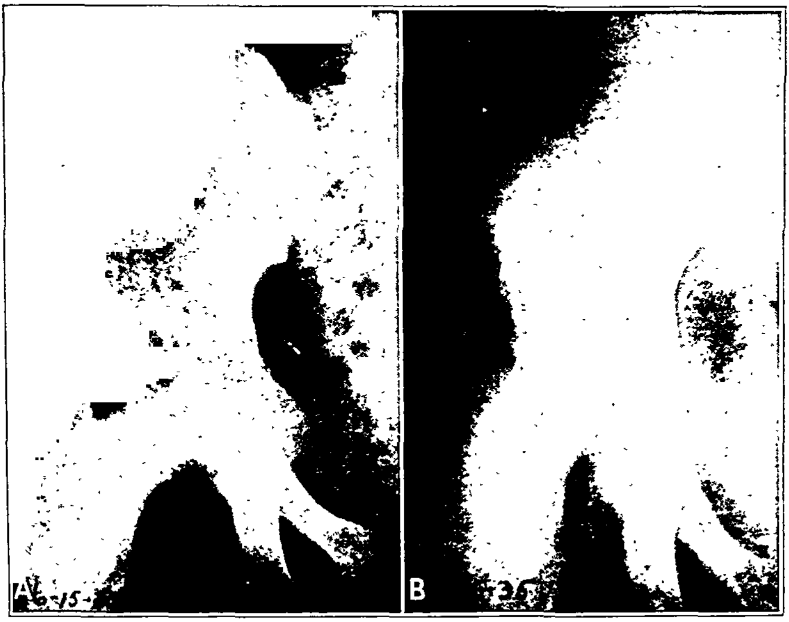

Fig. 5 (case 11).—*A,* roentgenogram of the pelvis, illustrating a prepuberty supracotyloid lesion twelve days after the onset of symptoms, which already involved the superior rim of the acetabulum. (The patient was referred by Dr. H. S. Conrad.) *B,* a roentgenogram taken two months later. The disease had extended to the wing of the ilium and some wandering of the acetabulum and head of the femur had occurred.

Case 13.—Gloria M., aged 11 years, was admitted to the hospital on April 24, 1936, with symptoms of three days' duration. She fell while roller skating and struck the left hip. That night she had a slight chill and fever, accompanied by anorexia and marked constipation. The fever and pain in the left hip persisted. On examination she was found to be mildly septic. The left hip was held in flexion and adduction, but was quite freely movable. There were marked tenderness over the lateral portion of the ilium and pubis and some tenderness in the left iliac fossa. The patient was placed in traction, and general measures were instituted. The white cell count was 6,000, and the sedimentation rate was rapid. The fever was sustained. On the fifth day definite infiltration appeared below the anterior crest of the ilium. The roentgenogram was still normal (fig. 7 *A*). The general condition was improved. A diagnosis of pyogenic osteomyelitis was made.

Operation—On April 29 an external subperiosteal abscess was drained just below the anterior crest of the ilium. The bone was very hemorrhagic but appeared slightly pale at the anterior metaphysial border. A fragment was removed for examination. The pathologic report was acute osteomyelitis, and staphylococci were recovered. A subacute course followed, and in about two weeks roentgenographic delineation of the lesion was noted (fig. 7 *B*), and partial resection (May 11) of the ilium was performed. The supracotyloid region was not involved, and an iliac abscess was now encountered and drained. Complete recovery followed subsequent treatment of a "silent" tibial metastatic lesion. Healing occurred in about five months.

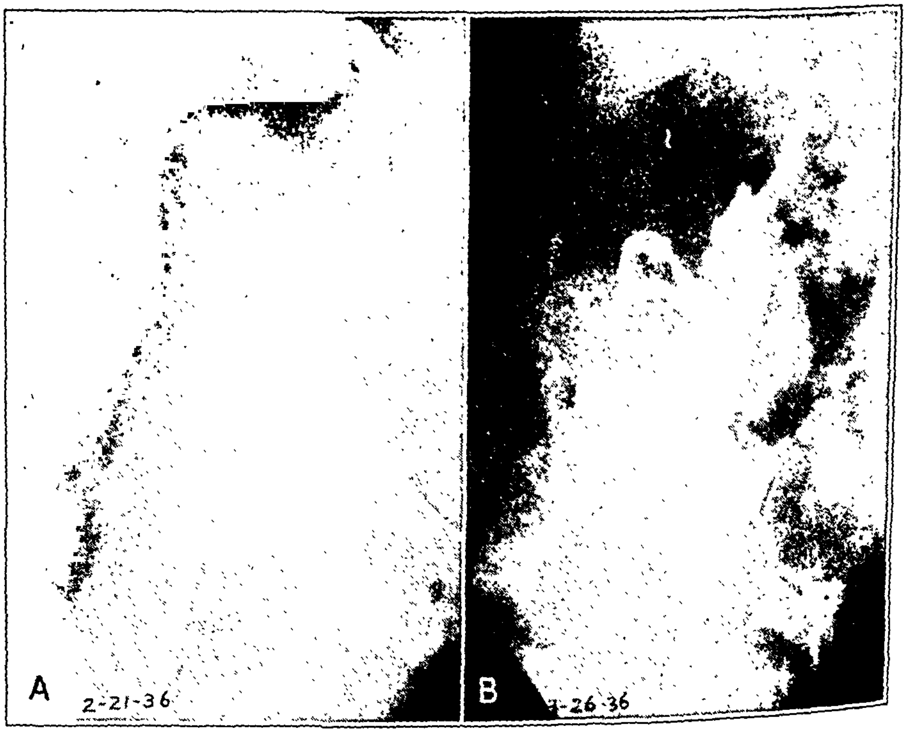

Fig. 6 (case 12).—Roentgenograms showing an iliac lesion involving the hip joint and femur of forty-one years' duration with a recent flare-up. The injection of iodized poppy-seed oil 40 per cent into the perirectal sinus revealed the extensiveness of the soft tissue abscess and the dangers of secondary infection from the rectum, especially after radical operation. (The patient was referred by Dr. Paul Forgrave.)

Osteomyelitis of the Ischium.—Case 14.—Russel C., aged 16 years, was admitted to the hospital on Nov. 2, 1933, with symptoms of eight weeks' duration. The onset began suddenly, with pain in the left hip, limpness and fever. This was aggravated by sitting and jarring. The patient had a series of boils three weeks previously. He had lost 27 pounds (12.2 Kg.) in weight. The leukocyte count

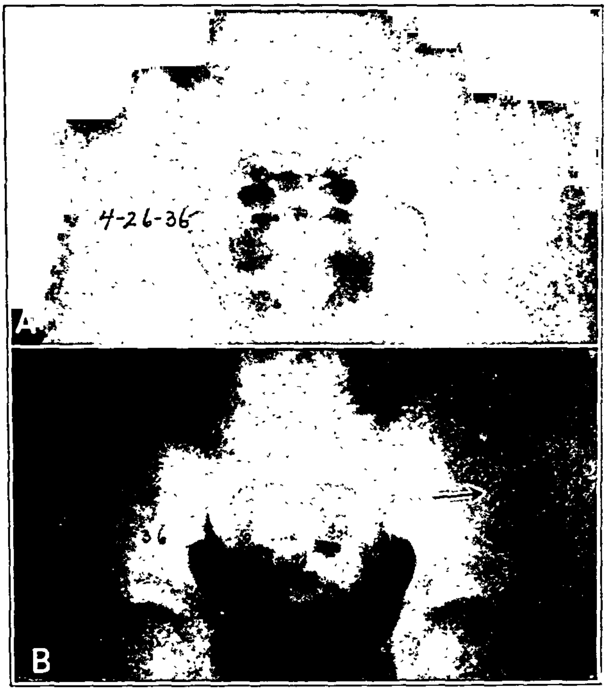

Fig. 7 (case 13).—*A*, roentgenogram of the pelvis five days after the onset of symptoms. No abnormal changes are demonstrated. *B*, a roentgenogram made twenty-one days after the onset. Destructive and productive changes appear at the lateral margins of the left ilium.

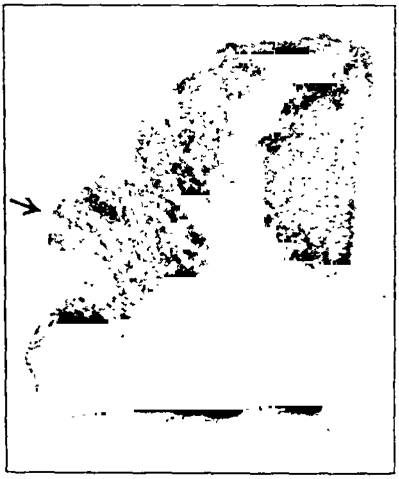

Fig. 8 (case 13).—Roentgenograms of the resected portion of the ilium twenty-two days after the onset of symptoms. The destructive process about the secondary epiphysial centers of activity is evident, although the child was only 11 years of age. The arrow points to the anterior superior spine. (Presented by courtesy of Dr. A. B. McGlothlan.)

was 14,000. There were occasional radiating pain in the left knee, and the hip and knee had drawn up. Examination revealed a well developed but moderately emaciated boy. The left lower extremity was held in 90 degrees of external rotation and 50 degrees of flexion. He held the left hip guardedly. The inguinal glands were enlarged, and there were no local signs of inflammation but some induration about the left ischiorectal fossa and definite tenderness over the left ischial tuberosity. Rectal examination revealed tenderness of the left ischium. The white cell count was 10,000. The roentgenograms showed a marked honeycombing and destructive process in the left ischium (fig. 9 *C* and *D*). A diagnosis of tumor or pyogenic osteomyelitis was made.

Operation.—Total resection was done in November 1933. There was no frank pus, but considerable necrosis and marked parosteal edema were present. There was no periosteal proliferation. The bone was hemorrhagic and shaggy and strongly suggested tumor formation. Staphylococcus aureus was recovered from the necrotic bone, and osteomyelitis was diagnosed pathologically. Histologic examination showed necrotic marrow and some cortical sequestration, but the cartilaginous portion of the ischium was well preserved. In spite of the predominance of bone absorption, production of new bone was nevertheless occurring. In some places the marrow was densely infiltrated by polymorphonuclear leuko-

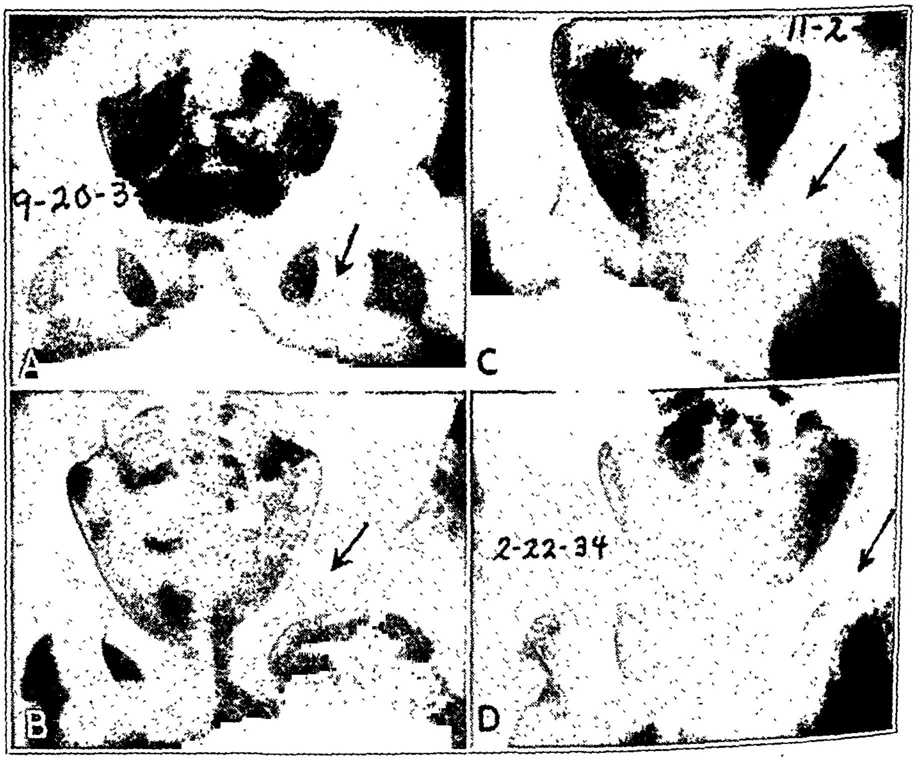

Fig. 9 (case 14).—Serial roentgenograms of the pelvis. In *A*, taken several days after the onset of symptoms, no ischiac pathologic process was noted. In *B*, taken about eight weeks after the onset of symptoms, the pathologic changes in the ischium simulated tumor rather than an inflammatory lesion. *C* was taken immediately after resection of the ischium and *D* about four months later, when regeneration was taking place.

cytes. The granulations rapidly changed into dense fibrous tissue, with almost immediate hyaline degeneration. While no frank pus was visible, there was nothing to indicate tumor formation.

The convalescence was uneventful. The wound healed in four months. The external rotation deformity of the hip present on admission awaits corrective osteotomy.

Case 15.—Hazel M., white, aged 6 years, was admitted to the hospital on Feb. 4, 1934, with symptoms of two days' duration. She began to limp suddenly two days before her admission to the hospital. She became ill rapidly and had a high fever, the temperature reaching 106 F. Several days before the onset she had an infected blister on the foot. On admission she was flushed and almost moribund. The hip was held in flexion but could be moved substantially. Pressure over the ischium on rectal examination caused the patient to wince even though she was practically unconscious. Aspiration in the region of the ischium with the patient under anesthesia gave negative results. (A tentative diagnosis of pyogenic osteomyelitis was made at this time.) The course was stormy, and several pyemic abscesses and also metastasis of the right fibula developed. In about six weeks the ischiatic lesion was definitely noted in serial roentgenograms (fig. 10), and the vulva was swollen.

Operation.—Total resection and removal of the floor of the acetabulum were done. On exploration medially and up toward the pubis, several cubic centimeters of frank pus were exuding from this region. The entire ischium was roughened. This reaction impressed one as being of a collateral nature. That portion of the ischium uniting with the descending portion of the pubis lifted out easily but did not appear to be definitely sequestrated. The floor of the acetabulum was, however, necrotic. Moderate shock ensued. Staphylococci were recovered, and the pathologic picture was that of pyogenic osteomyelitis. The changes in the infra-acetabular portions of the bone revealed changes chiefly of a collateral ischemic nature. The fibrous bone showed active bone formation leading to osteosclerosis. The cortical bone was alive, whereas the spongy bone showed necrosis. The acetabular region, the initial and primary seat of involvement, showed entire areas where the old spongy bone had disappeared and were occupied by dense fibrous bone, in greatest part osteoid. The small remnants of fatty bone marrow still showed inflammatory cellular infiltration. A diagnosis of subacute and chronic nonsuppurative osteomyelitis was made (osteomyelitis following invagination of old necrotic spongy bone by new bone apposition). The convalescence was uneventful, and the wound healed in three months with regeneration of the ischium (fig. 2 *C*).

Case 16.—Wanda S., aged 13 years, had symptoms of three months' duration, which were of subacute onset and course. On admission of the patient to the hospital it was difficult to localize the trouble accurately. In March 1933 the left hip was drained through a lateral incision, and no definite pathologic process was noted. In August 1933 the upper anterior portion of the ilium was exposed, and only sclerotic bone was encountered. The clinical course continued to show the presence of an active focus, which was finally located in the left ischium, after the vulva became .edematous.

Operation.—Total resection was done in November 1933. Through the usual approach the entire ischium was found to be necrotic and in a bed of pus. Staphyloccoci were recovered, and the pathologic diagnosis was chronic productive periostitis, subacute osteomyelitis and arthritis. The convalescence was uneventful, and the wound healed in three months, at which time the ischium had regenerated

Case 17.—Jule L., aged 16 years, was admitted to the hospital on July 22, 1935, with symptoms of eighteen days' duration. The onset was subacute and followed an indirect injury to the left hip. There was fever but no chills, and the pain was referred to the left hip and occasionally to the left knee medially. The patient appeared to be acutely ill. The left hip was held in flexion and some external rotation. Gentle manipulation elicited a fair range of motion, however. The entire left buttock was tense and tender and warm. Rectal examination revealed maximum tenderness over the ischium. The white cell count was 27,000, and the blood culture was negative. The roentgenogram is shown in figure 11. A diagnosis of pyogenic osteomyelitis was made.

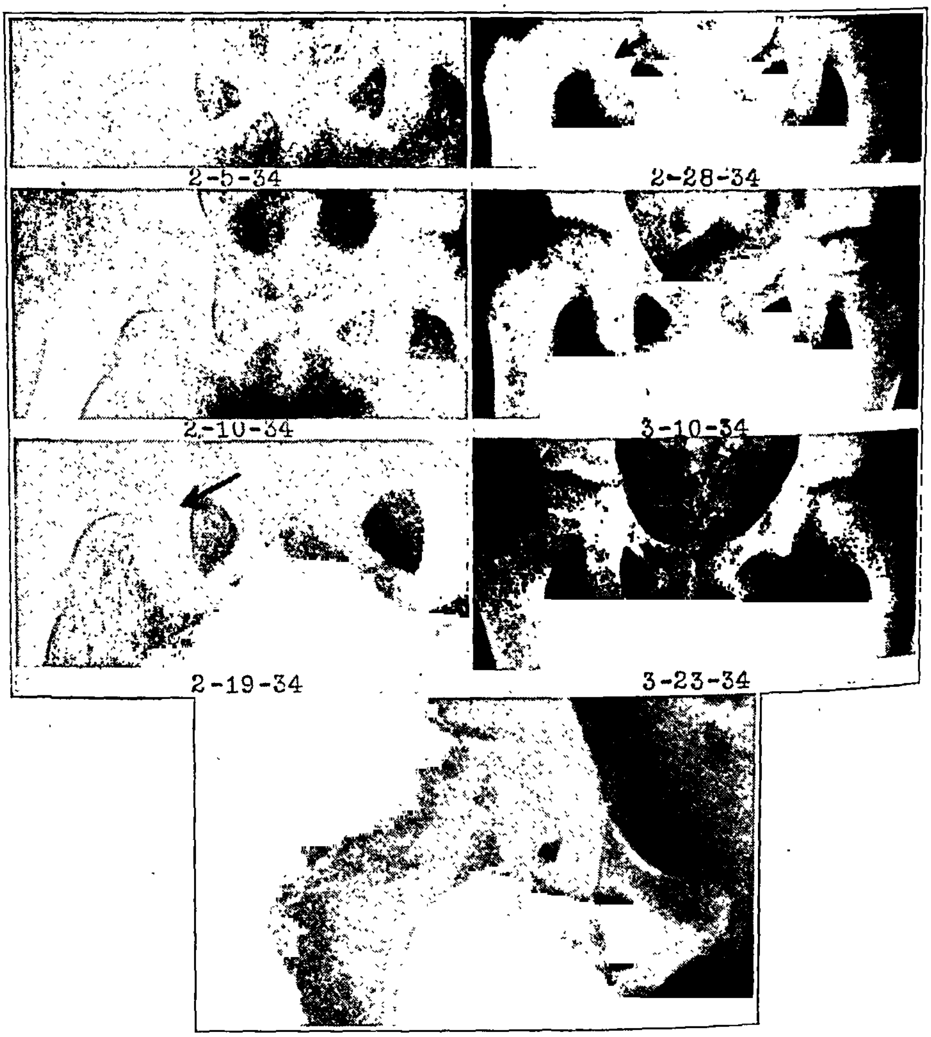

Fig. 10 (case 15).—Serial roentgenograms of the pelvis in a child, beginning three days after the onset of symptoms. Slight infra-acetabular changes were noted fourteen days later (2/19/34), but convincing evidence of destruction did not appear until thirty-six days after the onset of symptoms (3/10/34). The next picture was made after resection of the ischium and the last picture reveals regeneration about four months after operation.

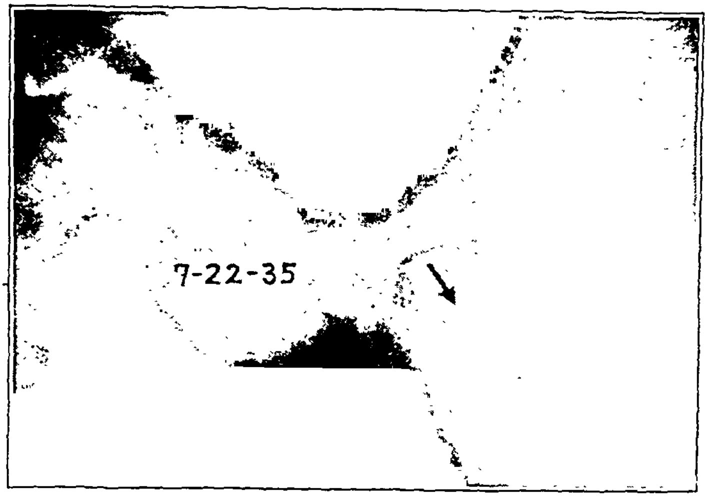

Fig. 11 (case 17).—Roentgenogram of the pelvis taken eighteen days after the onset of symptoms. The shadow of the soft tissue abscess predominates and obscures the skeletal ischiac changes. (The patient was referred by Dr. H. S. Forgave.)

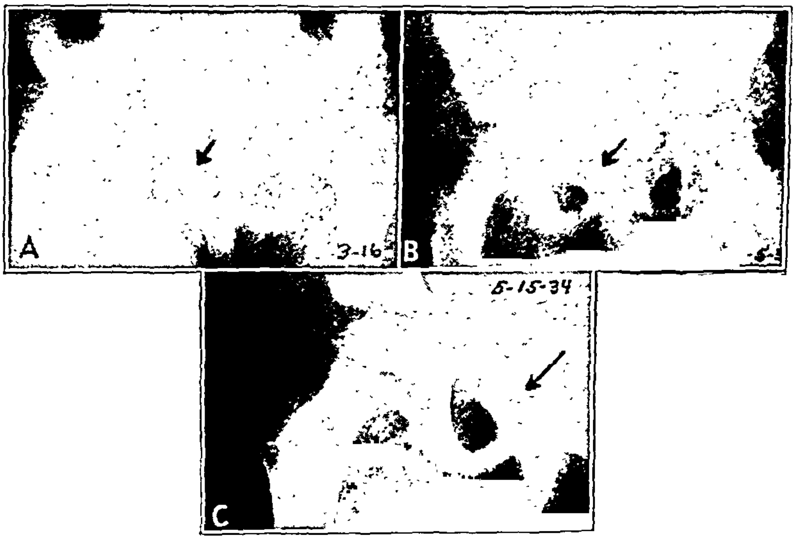

Fig. 12. (case 18).—*A*, roentgenogram showing a juxta-epiphysial pubic lesion three weeks after the onset of symptoms. The abscess and flexion of the hip blur the skeletal outlines. *B*, roentgenogram taken three weeks after operation. *C*, roentgenogram taken about six weeks later. There had been no extension, and the curetted bone is clear in outline.

Operation.—Total resection was done. A huge subgluteal collection of pus which involved the subgluteal bursa was evacuated. The ischium was bare owing to the stripping action of the pus. Most of the destruction was at the tuberosity, but the entire bone was removed because of the extensive purulent dissection already present. Staphylococci and streptococci were recovered. The pathologic diagnosis was subacute and acute pyogenic osteomyelitis. In spite of the radical resection, the patient's course continued to be of the low grade septic type, until the floor of the acetabulum was removed for more adequate drainage. The convalescence was then good, and healing occurred in about six months. There was residual ankylosis of the hip in good position.

Osteomyelitis of the Pubis.—CASE 18.—Phyllis S., aged 5 years, was admitted to the hospital on March 16, 1934, with symptoms of three weeks' duration. The condition was of sudden onset, with severe pain in the right groin associated with fever. She remained in bed with the right hip drawn up. She lost from 10 to 15 pounds (4.5 to 6.8 Kg.) in three weeks and appeared to be acutely ill and septic. The temperature was 104 F. There were marked tenderness over the inguinal ligament and some swelling of the right mons pubis and also the vulva of a lesser degree. The right hip was acutely flexed, but otherwise was normal. When the patient's attention was diverted, the hip could be moved. The white cell count was 32,000. The rectal examination (under anesthesia) revealed definite infiltration in the pubic region, the descending ramus and the medial wall of the right side of the pelvis. When the thigh was extended a fluctuating mass appeared in the right groin. The diagnosis made was pyogenic osteomyelitis as differentiated from appendical abscess.

Operation.—Drainage and curettage were done in March 1934. Through a curved incision about 3½ inches (8.9 cm.) long, cutting obliquely across the medial half of Poupart's ligament, an abscess cavity was entered just above Poupart's ligament and about 50 cc. of an odorless brownish creamy pus was found. Digital exploration showed this to be a granulation-lined subcutaneous abscess. About 100 cc. of thick green pus kept welling up from below Poupart's ligament, and this was found to be coming from Scarpa's triangle. Further digital examination of the right pubis showed a small localized necrotic area at the chondro-osseous border portion of the body of the pubis. This was carefully curetted out. Staph. aureus was recovered. The pathologic picture was that of acute osteomyelitis. Healing occurred in six weeks after an uneventful convalescence.

CIRCULATORY DISTURBANCES REFLEXLY INAUGURATED BY STIMULATION OF THE CELIAC PLEXUS

A PRELIMINARY REPORT

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Circulatory disturbances coincident with surgical manipulations in the upper part of the abdomen have frequently been described. A transitory initial rise in the blood pressure succeeded by a fall as a rule follows manipulation of the abdominal viscera. Recently, in a case in which a difficult cholecystectomy was performed, at the stage when operative manipulation was maximum, an unusual phenomenon was observed in the course of routine sphygmomanometry by the auscultation method. The blood pressure, which had remained constantly within normal limits with a difference of 60 mm. of mercury between the systolic and the diastolic level, suddenly became unobtainable for twenty minutes, although the peripheral pulse could still be palpated and was not materially altered in rate. At first, the mercury column being allowed to fall very slowly, a single beat was heard at about the level of the previous systolic pressure. Within a few minutes this single beat could not be obtained. It was further noted that when the operative manipulations had ceased, the normal auscultation sounds were again obtained and at a level comparable to the previous determinations. Thereafter, careful and frequent determinations on the blood pressure were made during all operations on the upper part of the abdomen. The phenomenon described was soon obtained in the course of another cholecystectomy and during gastric resection. The patients had been given morphine and atropine preoperatively. In an attempt to account for the circulatory disturbance noted, observations were made in the laboratory to determine the effects on the blood pressure curve obtained during intra-abdominal manipulations.

EXPERIMENTAL STUDY

Dogs were used for the experiments, and attempts were made to reproduce the same operative conditions. Preoperative medication consisted of 5 mg. of morphine sulfate and 0.1 mg. of atropine sulfate per kilogram of body weight

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administered subcutaneously one hour before anesthesia. Ether anesthesia was then induced by the open cone method, and an endotracheal tube was passed through the mouth into the trachea and made air tight by inflating a cuff surrounding it. This tube was connected to a rebreathing bag, and a canister containing soda lime was inserted between the two so that the technic of carbon dioxide absorption [1] could be maintained. Ether and oxygen were supplied to the system by means of a Foregger metric machine. The blood pressure was recorded from a cannula inserted into the femoral artery and connected to a mercury manometer which registered on a kymograph. Respirations were recorded at the same time by means of a pneumograph applied about the thoracic region.

The peritoneum was opened by a long midline incision. Traction on the various viscera and intra-abdominal exploration resulted in circulatory disturbances consisting of a small rise in the mean arterial blood pressure and a slight reduction in the pulse pressure. Traction on the gallbladder, as shown by Brewer and Luckhardt,[2] was followed by apnea (chart 1 *B*), and a slight rise in the blood pressure was recorded. Exploration in the region of the solar plexus and especially compression of the celiac ganglion gave an immediate response characterized by a marked reduction in the pulse pressure without a fall in the mean blood pressure (chart 1 *C*). The diminution of the range between the systolic

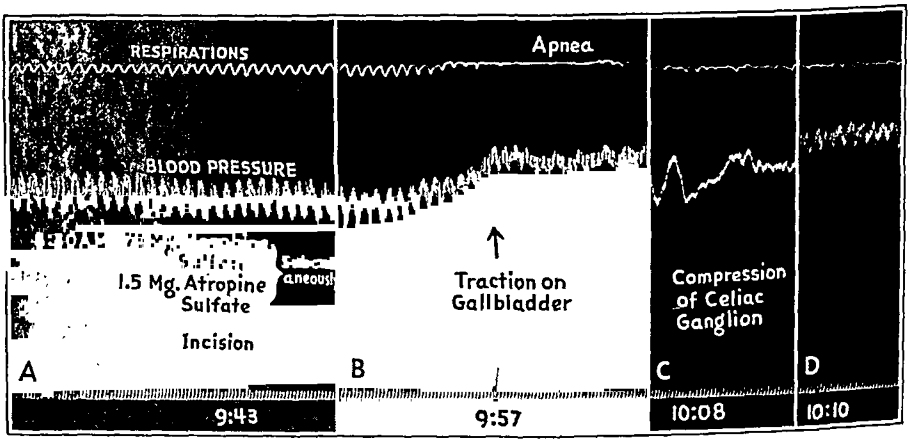

Chart 1.—Serial sections from an experiment on dog 34, which weighed 15 Kg. At 8: 30 a. m. 75 mg. of morphine sulfate and 1.5 mg. of atropine sulfate were administered subcutaneously. At 9: 43 a. m., when the initial incision was made, the blood pressure was normal, as indicated in *A*. In *B* are shown the effects of traction on the gallbladder at 9: 57 a. m., which included apnea, a rise in the mean blood pressure and a reduction in the pulse pressure. Compression of the celiac ganglion at 10: 08 a. m. brought about a marked reduction in the pulse pressure and no appreciable change in the mean blood pressure, as shown in *C*. After the compression of the celiac ganglion was released at 10: 10 a. m., the pulse pressure recovered, as shown in *D*.

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1. Waters, R. M.: Utility of Carbon Dioxide Absorption from Anesthetic Mixtures, Anesth. & Analg. **3**:20 (Feb.) 1924.

2. Brewer, N.; Luckhardt, A. B.; Lees, W. M., and Bryant, D. S.: Reflex Closure of the Glottis by Stimulation of Afferent (Visceral) Nerves, Anesth. & Analg. **13**:257, 1934.

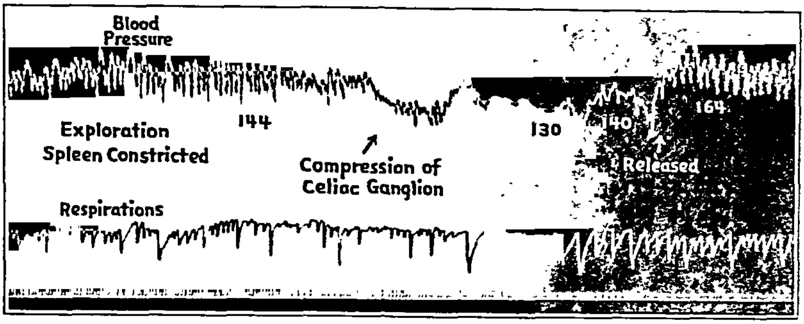

Chart 2.—A tracing showing the reflex in its entirety. Atropine sulfate was given previously.

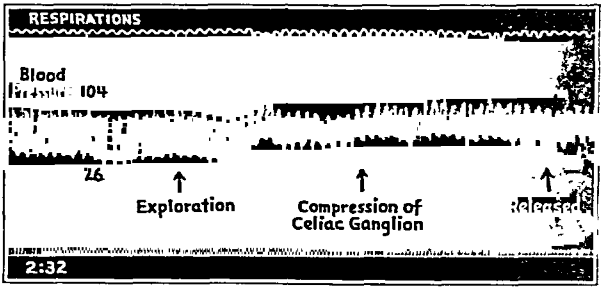

Chart 3.—A tracing showing the reflex when atropine sulfate was not administered.

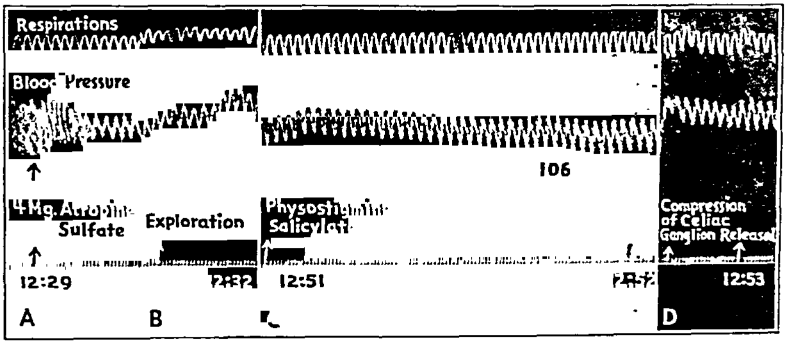

Chart 4.—Serial sections from an experiment on dog 201, which weighed 22 Kg. One hundred milligrams of morphine sulfate was administered at 10:30 a. m. In *A* is shown the immediate reduction of the pulse pressure after the intravenous injection of 4 mg. of atropine sulfate at 12:29 p. m. Intra-abdominal exploration at 12:32 p. m., indicated in *B,* was followed by compression of the celiac ganglion. The intra-abdominal exploration caused a reduction in the pulse pressure and a rise in the mean blood pressure, while compression of the celiac ganglion caused further and more marked reduction in the pulse pressure and no change in the mean blood pressure. After twenty minutes with no improvement in the pulse pressure, an intravenous injection of physostigmine salicylate at 12:51 p. m. readily caused a return of the pulse pressure, as shown in *C.* Intra-abdominal exploration was followed by compression of the celiac ganglion after the administration of physostigmine salicylate at 12:53 p. m., as indicated in *D.* The first procedure caused only a slight reduction in the pulse pressure and a slight rise in the mean blood pressure. The latter procedure caused a very slight further reduction in the pulse pressure and no change in the mean blood pressure.

and the diastolic pressure became so marked that the pulse pressure practically disappeared. At the same time the abdominal muscles became more tense, and the intestines protruded from the wound. On releasing the compression the pulse pressure returned (chart 1 *D*). Similar tracings were secured following the application and release of pressure on the celiac ganglion (chart 2). This reaction was repeated in several dogs prepared and experimented on in the same manner.

It was further noted that when atropine sulfate was not administered the production of this reflex was either absent or greatly diminished, the pulse pressure falling but slightly (chart 3). However, if a dog which had not received atropine sulfate and did not show this reflex was given an intravenous injection of the drug a definite reduction in the pulse pressure (chart 4 *A*) would immediately result, and compression of the celiac ganglion would then be followed by a further reduction in the pulse pressure (chart 4 *B*), which would be maintained for a long time. Furthermore, if physostigmine salicylate was given intravenously the pulse pressure was markedly increased (chart 4 *C*). After physostigmine salicylate was administered, efforts to elicit this celiac plexus reflex would result in only a slight reduction of the pulse pressure (chart 4 *D*).

It was therefore evident that compression of the celiac ganglion caused a reflex reduction in the pulse pressure and that paralyzing the vagus nerves with atropine sulfate intensified the reflex, whereas stimulation of these nerves with physostigmine salicylate prevented entirely or reduced an already existing reflex. It is interesting to note that Capps and Lewis,[3] in their work on pleural reflexes, have found that stimulation of the pulmonary vagus nerves (instead of their paralysis) is followed by a "cardio-inhibitory reflex, in which the heart is slowed and the pulse tracings make violent excursions, with a great range between systolic and diastolic pressure."

Further experimental studies to show the mechanism of this reflex are in progress and will be reported at a later date.

SUMMARY

Stimulation of the celiac plexus when atropine sulfate has been previously administered produces a marked reduction in the pulse pressure with maintenance of the mean arterial blood pressure.

Stimulation of the celiac plexus when atropine has not been administered previously causes little or no change in the pulse pressure.

Manipulations in the upper abdominal cavity cause a reduction in the pulse pressure, especially when atropine sulfate has been given previously.

Administration of physostigmine salicylate reduces the reflex.

477 First Avenue.

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[3] Capps, J. A., and Lewis, D. D.: Pleural Reflexes, Surg., Gynec. & Obst. **7**:243, 1908.

SIXTY-THIRD REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Congenital Dislocation of the Hip.—Van Gorder[1] reviews the end-results in 58 cases of dislocation of the hip (73 hips) in which treatment was given at the Massachusetts General Hospital during the period from 1923 to 1933. Sixteen of the hips were treated by closed reduction. The results in 10, or 62 per cent, were rated as excellent; *i. e.*, there were a negative Trendelenburg sign, normal motion and no limp, shortening or atrophy. The results in 4, or 25 per cent, were rated as good; i. e., there were a slight limp, a positive Trendelenburg sign, excellent function and no disability. The results in 2, or 12.5 per cent, were rated as fair. Fifteen hips were treated by open reduction. The results in 1 were rated as excellent and in 3 as poor. Bony ankylosis occurred in 2, and a stripping of all structures from the neck and trochanters was done on the last 2 hips preliminary to heavy traction and open reduction. The 8 hips treated by open reductions plus a shelf operation showed no excellent results; the results in 2 were rated as good, in 1 as "fair" and in 2 as poor, and bony ankylosis occurred in 3. Sixteen hips treated by

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This report of progress is obtained from a review of 144 papers selected from 296 titles relating to orthopedic surgery and appearing in the medical literature approximately between Nov. 1, 1936, and March 1, 1937. Only those which indicated progress were selected for review.

[1] Van Gorder, G. W.: New England J. Med. **215**:613 (Oct. 1) 1936.

a shelf operation alone showed no excellent results; the results in 8, or 50 per cent, were rated as good, in 4, or 25 per cent, as fair and in 4 as poor.

Summarizing these statistics in a different way: Good functional results were obtained in 88 per cent of the hips treated by closed reduction, in 27 per cent of those treated by open reduction, in 25 per cent of those treated by open reduction plus a shelf operation and in 50 per cent of those treated by a shelf operation alone. While the author feels that these results are far from satisfactory, he points out that two thirds of the patients in this study were over 5 years of age when treated.

Congenital Hallux Valgus.—Hoffmann[2] reports 4 cases of congenital deviation of the second phalanx of the great toe and was able to find 4 similar cases described in the literature. The author considers the condition as a congenital arrest in development in the epiphysis of the phalanx. Correction was obtained by a wedge osteotomy of the proximal phalanx of the big toe.

Brittle Bones and Blue Scleras in 5 Generations.—Blue scleras, fragile bones, a tendency to deafness and marked relaxation of the ligaments constitute a clinical entity according to Hills and McLanahan.[3] Data concerning 51 persons in 5 generations, all traced back to a common female ancestor, revealed that 27, or nearly half, were affected; 60 per cent were females. Deafness was manifest in 57 per cent. The blue sclera is generally attributed to thinness of the sclerotic coat, through which the choroid shines. The fractures are not likely to be present at birth but appear throughout childhood until puberty is reached. Union is prompt and complete. The etiology is unknown, but the fact that the fractures appear to cease at puberty would lead one to suppose that approach along endocrine lines offered greatest promise.

DISTURBANCE OF GROWTH

Tibia Vara.—Thirteen new cases and reports of 15 collected from the literature are reviewed by Blount[4] to illustrate the occurrence of an osteochondritis similar to coxa plana and Madelung's deformity but located at the medial side of the proximal tibial epiphysis. The resulting abrupt angulation into varus with back knee and internal rotation of the leg is usually confused with rickets. The roentgenographic picture and the pathologic changes are like those of coxa plana and similar to those of chondrodysplasia but are quite different from those of rickets. The changes may appear in the first year or two of life (infantile type) as a developmental exaggeration of the normal, with sloping epiphysis and beaklike, recurving metaphysis. Similar deformity may occur just before puberty (adolescent type), secondary probably to local trauma or possibly to infection. The age at which the deformity is observed is more important than the causative factor in determining the roentgenographic appearance. The roentgenographic picture presented by the infantile type gradually changes to that presented by the adolescent type, so that later the two can be distinguished only by the history. Treatment should be directed toward the mechanical relief of strain until the deformity is stationary or until the epiphysis is closed. Simple osteotomy is desirable in the correction of marked deformity. If it is done before the angulation becomes stationary, some degree of recurrence may be anticipated.

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[2] Hoffmann, H.: Ztschr. f. Orthop. **65**:353, 1936.

[3] Hills, R. G., and McLanahan, S.: Brittle Bones and Blue Scleras in Five Generations, Arch. Int. Med. **59**:41 (Jan.) 1937.

[4] Blount, W. P.: J. Bone & Joint Surg. **19**:1, 1937.

TUBERCULOSIS

Multiple Arthritis in Tuberculous Subjects.—Collins and Cameron[5] sound a warning against the too early acceptance of a tuberculous etiology in cases of insidious arthritis occurring in presumably tuberculous patients, as this often results in prolonged and expensive immobilization, which is prejudical to subsequent recovery of function. They suggest that in all such cases expectant treatment should be adopted. This should consist of maintenance of general hygiene and rest in bed without immobilization until unequivocal evidence of the tuberculous or nontuberculous nature of the joint appears or is obtained by examination or by biopsy of material obtained by aspiration.

Glutathionemia in Tuberculosis of Bones.—Altschuler[6] studied the glutathione content of the blood from children with tuberculosis of the bones and joints. The more severe the tuberculous lesion, the higher were the values for glutathione in the blood. The author feels that fluctuations in the glutathione content of the blood assisted in estimating the course of the disease. A review of the literature is given.

Result of Spinal Fusion in Tuberculous Spondylitis.—Grigorescu and Vasiliu[7] report on 82 of 182 cases of tuberculous spondylitis in which an Albee fusion operation was performed. Postoperative fixation consisted of three months of rest in a plaster bed followed by the use of back supports. After six months the patients were permitted to return to their occupation. Twenty-four were well from seven to nine years after the operation; healing was taking place in 50 with considerable improvement from three to four years after the operation. In eight of those with abscesses, the abscesses had healed. In 2 there was no change and the abscesses persisted. One with paraplegia was somewhat improved. Four had died from three months to five years after the operation. One died of sepsis four days after the operation.

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[5] Collins, D. H., and Cameron, C.: Brit. J. Surg. **24**:272, 1936.

[6] Altschuler, M. M.: Acta tuberc. Scandinav. **10**:370, 1936.

[7] Grigorescu, I. I., and Vasiliu, A.: Beitr. z. klin. Chir. **164**:1, 1936.

Use of Biopsy Specimens Obtained by a Punch in the Diagnosis of Tuberculosis of the Knee Joint.—In connection with the arthroscope, which resembles a cystoscope and is used for direct observation of the knee joint, Burman and his co-workers[8] have developed a punch for obtaining biopsy specimens from the knee joint. It is inserted through the same puncture hole used for the arthroscope. The specimen is secured blindly, although the arthroscope is first used for localization. In 8 cases of proved tuberculosis of the knee, the diagnosis was made in 6 on the basis of specimens secured with this instrument. This method is offered as another diagnostic test for tuberculosis of the knee and is considered by the authors as preferable to the radical method of securing a biopsy specimen, as advocated by Hibbs.

OSTEOMYELITIS

Osteomyelitis of the Bones of the Hand.—Osteomyelitis of the bones of the hand secondary to infection of the soft tissue is often treated radically by guttering or by removal of the bone. Koch,[9] whose experience is extensive, condemns such radical surgical methods. He states:

> The essential factors in the treatment of osteomyelitis of the bones of the hand are adequate drainage of the overlying soft parts, cleanly surgical care, and avoidance of trauma—by irritating chemicals, by addition of infection from without, and, particularly, by the use of curette and chisel. If death of bone takes place a line of demarcation forms and the necrotic bone, if it is not extruded spontaneously, can be removed without trauma. To attempt to determine a line of demarcation by surgical intervention too frequently results in destruction of living bone and extension of infection, and often makes recovery of the affected bone impossible.

POLIOMYELITIS

Humoral Antibodies and Resistance to Poliomyelitis.—Sabin and Olitsky[10] found that monkeys recovering from a paralytic attack of poliomyelitis acquired humoral antibodies slowly two months after the attack. Convalescent monkeys showed resistance to reinfection by the nasal route long before antibodies appeared in their serum. Vaccinated monkeys often remained susceptible to nasal infection when their serum neutralized the virus. Humoral antibodies do not seem to have the same significance in vaccinated monkeys as in monkeys recovering from an attack of poliomyelitis.

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[8] Burman, M.; Finkelstein, H., and Mayer, L.: Am. Rev. Tuberc. **34**:663, 1936.

[9] Koch, S. L.: Surg., Gynec. & Obst. **64**:1, 1937.

[10] Sabin, A. B., and Olitsky, P. K.: J. Exper. Med. **64**:739, 1936.

CHRONIC ARTHRITIS

Fibrositis.—Slocumb [11] states that "fibrositis" is the commonest form of acute or chronic "rheumatism." The term appears in the foreign literature frequently but is seldom seen in the American literature. The author, nevertheless, believes that a condition exists which should be referred to as "fibrositis" rather than by any other term. Although in most cases the exact etiology is unknown, fibrositis is believed to be due to some unidentified infection or toxin. He believes that primary fibrositis should include (1) "myositis;" (2) "bursitis;" (3) periarticular fibrositis, or so-called "capsular rheumatism;" (4) tendinous fibrositis, which leads to Dupuytren's contracture of the palm; (5) perineural fibrositis, of which "sciatica" and "brachial neuralgia" are the common types, and (6) panniculitis. In the first stage of the process there is a low grade inflammatory serofibrinous exudate with proliferating fibroblasts and newly formed blood vessels; in the second stage, indurated, tender thickened tissue or subcutaneous nodules may be produced which may show dense inflammatory hyperplasia of fibrous tissue, thickened blood vessels and inflamed nerve fibrils without leukocytic reaction; in the third stage, when the inflammatory stage has passed, indurations may disappear or remain as painless nodules or capsular thickening which may affect such regions as the shoulders or the palms. The author feels that the differential diagnosis between these two conditions lies in the abundant indirect evidence of the persistent integrity of the joint cavity in fibrositis; that is, the disease is at the joint and not within the joint. Laboratory findings revealed little or no change in the sedimentation rate in cases of periarticular fibrositis in contrast to the rapid rate in cases of atrophic arthritis. Likewise, roentgenographic findings are demonstrated only in cases of atrophic arthritis. Finally, the author feels that when objective changes, systemic manifestations and alterations of laboratory findings, known to be relatively consistent in cases of atrophic arthritis, remain persistently absent, the arthralgia, stiffness and articular thickening can be, with no little confidence, ascribed to periarticular fibrositis, and the fear of impending arthritis can be laid aside.

THE SHOULDER

Scaglietti [12] discusses obstetric lesions of the shoulder thoroughly and describes the method of therapy as used by Putti. The article is based on a study of 199 cases in which therapy was given at the Instituto Rizzoli from 1899 to July 1935. The condition was unilateral in 93 per cent of the cases and bilateral in 6.5 per cent. In 62 per cent of the total number the right shoulder was involved. Conservative treatment was used in 75 per cent of the cases and surgical treatment in 25 per cent. The cases were divided into three groups: those of obstetric trauma of the joint or the superior humeral epiphysis or distortion of the joint or fracture of the clavicle (62 cases), those of pure obstetric paralysis consisting of trauma to the nerve root, subdivided into paralysis of the upper part of the arm, the lower part of the arm and the whole arm (22 cases) and a mixed group of cases in which both articular damage and injury to the nerve were present (14 cases). In 101 cases of the series there was no record as to the exact type. The classification of these injuries depended on the results of the physical, roentgenographic and electrical examinations of the muscles. The roentgenographic studies showed that in the group of cases of trauma to the joint the normal angle of the head of the humerus as superimposed over the condyles was increased from a position of internal rotation of 20 degrees to an abnormal one of 40 degrees or more. Therefore, with the head of the humerus pointing posteriorly and the whole arm internally rotated, the suprascapular and infrascapular muscles are elongated while the pectoral and subscapularis muscles are contracted. Because of this complicated lesion in the first group of cases, Putti carried out the surgical therapy in two stages. First, a Sever operation was done with severance of the contractured muscles and capsule. The arm was put up in abduction and external rotation for two months. Second, by this approach osteotomy was done through the neck of the humerus, and with elbow flexed at 90 degrees the lower part of the arm was internally rotated to a neutral position. With the arm abducted 45 degrees a second shoulder spica was applied and left on for two months. The treatment in the second group of cases consisted primarily of splinting and physical therapy. Primary nerve sutures were performed in a small series of cases with poor results. The treatment in the third group depended on the site of greatest deformity. The illustrations show excellent operative results in the first group of cases.

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[11] Slocumb, C. H.: J. Lab. & Clin. Med. 22:56, 1936.

[12] Scaglietti, O.: Chir. d. org. di movimento 22:183, 1936.

[Ed. Note.—This is a splendid, thorough, long article and is well illustrated. Though previously emphasized by authors, the fact that obstetric paralysis of the shoulder is frequently joint trauma essentially and not pure paralysis is often forgotten. This article merits careful reading, and the therapy suggests trial by others.]

PERIPHERAL VASCULAR DISEASE

Intermittent Venous Occlusion for Treatment of Peripheral Vascular Disease.—Collens and Wilensky[13] report the effect of treatment in peripheral vascular disease by means of intermittent venous occlusion.

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[13] Collens, W. S., and Wilensky, N. D.: The Treatment of Peripheral Obliterative Arterial Diseases, J. A. M. A. **107**:1960 (Dec. 12) 1936.

They used a pneumatic cuff in the lower third of the femur by means of which from 60 to 80 mm. of mercury was applied in alternating periods of two minutes every two hours. In obliterative disease, e. g., arteriosclerosis, relief is obtained, but treatment must be continued indefinitely. Pain was relieved, ulcers were healed and the walking capacity was increased.

NEOPLASMS

Treatment of Giant Cell Tumors of Bone.—Peirce and Lampe[14] report the results of treatment of 40 patients with giant cell tumor of the bone. Five refused treatment and 6 were treated by preoperative irradiation, surgical intervention and postoperative irradiation, 9 by surgical intervention and postoperative irradiation, 4 by surgical intervention alone and 15 by roentgen irradiation alone. The authors conclude that adequate treatment with roentgen rays or adequate surgical intervention offers as much as the two methods combined. Adequate curettage in anatomically accessible areas has given good functional results. Roentgen treatment offers symptomatic relief and often leads to anatomic repair.

Giant Cell Tumor of the Patella.—Sorge[15] was able to find reports of only 15 cases of giant cell tumor of the patella in the literature. He reports 1 additional case. Treatment consisted in complete removal of the patella and a plastic reconstruction of the quadriceps tendon. The functional and cosmetic results were satisfactory.

Synovial Sarcoma.—Synovial sarcoma is a rare form of malignant tumor of the extremities. Knox[16] reports 3 new cases and includes abstracts of 19 reports in the literature. The tumor arises from a joint, bursa or tendon. It has a characteristic microscopic appearance from which a diagnosis can be made; it is resistant to irradiation. No permanent cure by amputation has yet been recorded.

A series of 117 cases of tumor of the bone in children is presented by Goin and Carroll.[17] In 8.6 per cent the growth was malignant. A classification of bone tumors is offered, in which they are placed in three main groups: (1) those arising from osteogenic elements, (2) those arising from tissues resident in the bone and (3) those of metastatic origin. A review of the characteristics of the various types of tumor of the bone is made, and the results of treatment in the authors' cases are outlined. The writers recommend that a biopsy specimen be secured by aspiration in every case in which a tumor is suspected, and they offer a plan of approach to the diagnosis of the various types of tumor by roentgen examination.

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[14] Peirce, C. B., and Lampe, I.: Giant Cell Bone Tumor, J. A. M. A. **107:** 1867 (Dec. 5) 1936.

[15] Sorge, E.: Riv. di chir. **2:**399, 1936.

[16] Knox, L. C.: Am. J. Cancer **28:**461, 1936.

[17] Goin, L. S., and Carroll, R. L.: Radiology **27:**261, 1936.

Hodgkin's Disease with Osseous Involvement.—Dresser and Spencer [18] present a series of 66 cases of Hodgkin's disease with involvement of the bone. The greatest number of these occurred in persons in the third and fourth decades, and the most frequent location was in the spine, pelvis and femur. The incidence of involvement of the bones in Hodgkin's disease as demonstrated roentgenographically is considered to be about 10 per cent, although it is found to be higher at autopsy. Involvement of the bones in Hodgkin's disease is usually considered to occur late, but in 16 of the 66 cases studied the lesions caused the presenting symptoms. The roentgenographic picture usually simulates that of a metastatic malignant process, but it may be confused with the roentgenographic picture of Ewing's tumor, osteogenic sarcoma, bone cyst or osteomyelitis. There is never an entirely characteristic roentgenographic picture; therefore, it must be considered in any unusual lesion. Hodgkin's disease with involvement of the spine often causes collapse of the vertebral body, and when the long bones are involved a pathologic fracture may occur. Involvement of bone may be by direct invasion or by metastasis to the blood stream. Primary Hodgkin's disease of bone has never been observed. The response of the lesion in the bone to irradiation is variable and in general is less satisfactory than that of lesions elsewhere. There is often striking relief from pain, although the prognosis is hopeless. In 36 cases the average duration of life after the first symptoms was three and one-half years; the average duration of life in these cases after the lesion of the bone became evident was eleven months.

Sun Ray Hemangioma of Bone.—Anspach [19] discusses a case of hemangioma of the skull in a child of 11 and then considers the roentgenographic appearance of this type of tumor in different bones. In flat bones a hemangioma usually gives a "sun-ray" or "sunburst" appearance of radiating bone spicules. In proved cases of this tumor in the flat bones there have been strikingly similar patterns. In long bones the sun-ray appearance is not as typical or as constant, and the "soap-bubble" appearance occurs about as frequently. In the spine the predominant features are vertical streaks of parallel densities. The author concludes that although hemangioma is not common it must be suspected in any case of bone tumor showing "sun-ray" spicules, whether occurring in flat or in long bones. No tumor of this sort should be removed without a biopsy first. Treatment should be conservative and consist of roentgen or radium therapy.

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[18] Dresser, R., and Spencer, J.: Am. J. Roentgenol. **36**:809, 1936.

[19] Anspach, W. E.: Sunray Hemangioma of Bone, with Special Reference to Roentgen Signs, J. A. M. A. **108**:617 (Feb. 20) 1937.

MISCELLANEOUS

Ischiopubic Osteochondritis.—Torgersen[20] reports 2 instances of ischiopubic osteochondritis in children 8 and 9 years old. Roentgenograms showed slight swelling and sclerosis of the junction between the lower ramus of the pubis and the ischium. The symptom was pain in the inguinal region on walking. The author believes that mechanical factors played a part in causing the lesion. The treatment consisted in preventing overexertion and in correcting static defects. The literature on this lesion is reviewed.

Cervical Rib and Anterior Scalenus Syndrome.—Flothow[21] reports irritation of the brachial plexus from abnormalities in the supraclavicular triangle. Whether cervical ribs are present or not, section of the anterior scalenus muscle has given relief and is safer than removal of the cervical ribs.

New Roentgenograms of the Skeleton.—Zwerg[22] mentions new positions for obtaining valuable roentgenographic information on bones. These are: (1) a transthoracic lateral view of the upper end of the humerus, (2) a transpelvic lateral view of the upper end of the femur, the other hip being flexed 90 degrees to get it out of the field, (3) a lateral view of the cervical portion of the spine, taken at a distance of 6 feet (183 cm.), a flat casette being used, and (4) a view of the sternum and patella taken with the patient prone rather than supine.

Disk-Shaped Lateral Meniscus with Snapping Knee.—Four cases of disk-shaped lateral meniscus are described by Middleton.[23] He attributes the snapping noise which is associated with movement in this condition to the presence of a ridge dividing the disk into anterior and posterior facets, which contact with the femoral condyle in extension and flexion, respectively. When flexion is being carried out the ridge is pushed back till the movement is almost complete, when it escapes forward with an audible click. The reverse movement of the disk takes place during extension. When the disk-shaped meniscus is fractured, the click takes place over the fractured edge.

Os Acromiale and Its Significance.—The os acromiale has long been recognized by anatomists as an ununited end of the acromium. Schär and Zweifel[24] report 22 cases of this anomaly. Occasionally local pain is felt either spontaneously or after trauma. The condition is usually on the right side and is more frequent in the male. Its medicolegal significance lies in its resemblance to an old fracture line. Roentgenograms of the axillary region with the humerus in 90 degrees of abduction reveal the anomaly clearly.

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[20] Torgersen, J.: Norsk mag. f. lægevidensk. **97**:951, 1936.

[21] Flothow, P. G.: West. J. Surg. **44**:570, 1936.

[22] Zwerg, H. G.: Arch. f. klin. Chir. **185**:578, 1936.

[23] Middleton, D. S.: Brit. J. Surg. **24**:246, 1936.

[24] Schär, W., and Zweifel, C.: Beitr. z. klin. Chir. **164**:101, 1936.

[Ed. Note.—There is still confusion regarding the diagnosis of this lesion, often by expert roentgenologists. The lesion is not rare, and attention should be called to it.]

Anomalous Bones of Wrist and Foot.—Watkins [25] lists and describes 12 anomalous conditions in the wrist and 12 in the foot which might be wrongly considered as due to injuries to these parts. The most important and confusing anomalies in the wrist were congenitally bipartite scaphoids and congenitally ununited styloids of the ulna. In the foot the most important variations were the os trigonum, the tibiale externum (separate and unfused tuberosity of the scaphoid) and a secondary os calcis.

Osteopoikilosis.—Holly [26] reports 4 cases of osteopoikilosis. Roentgenograms showed multiple discrete symptomless small areas of increased density in the bones of the extremities. The lesions occurred in a mother, a daughter and two sons, who were studied for five years. The author concludes from his observations that, as previously shown, the disease is familial. The islands of condensation are not constant; in the adult they may entirely disappear. In the child new areas appear with the growth of bone, which may entirely disappear as the child grows or may increase in size as bony development progresses. There is no variation in the uric acid content of the blood or the calcium-phosphorus metabolism.

ORTHOPEDIC OPERATIONS

Tendon Transplantation in Radial Paralysis.—Bonola [27] describes 3 cases of old paralysis of the radial nerve in which the treatment consisted of transplantation of tendons from the antagonistic muscles. All of the old operative procedures are reviewed. In the 3 cases described the operation consisted of modified insertion of the flexor carpi radialis longus tendon into the extensor tendons of the thumb and fingers. Usually the flexor carpi ulnaris tendon is inserted into the extensor tendons of the second to the fourth finger and the flexor carpi radialis tendon into the abductor longus and extensor tendons of the thumb. One case is illustrated in which apparently good results were obtained.

Hallux Valgus; Comparison of Two Operations.—Lloyd [28] reports 20 cases of bilateral hallux valgus in which different operations were performed on the two sides. On one side the head of the metatarsal bone was excised, and on the other, the base of the phalanx and the exostosis of the metatarsal bone. From the patient's replies at the end of from one to three years, it seems there is no choice between the operations as a means of relieving the pain of hallux valgus.

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[25] Watkins, W. W.: Anomalous Bones of Wrist and Foot in Relation to Injury, J. A. M. A. **108**:270 (Jan. 23) 1936.

[26] Holly, L. E.: Am. J. Roentgenol. **36**:512, 1936.

[27] Bonola, A.: Chir. d. org. di movimento **22**:239, 1936.

[28] Lloyd, E. I.: Brit. J. Surg. **24**:341, 1936.

A New Operation for Hallux Valgus.—According to Girdlestone and Spooner,[29] hallux valgus consists of valgus of the proximal end of the phalanx and varus of the first metatarsal bone, with splayfoot. The commoner types of operation for hallux valgus are: (1) resection of the head of the first metatarsal bone and (2) hemiphalangectomy, which reduces the deformity but does not improve the splayfoot or the metatarsalgia, if present. These difficulties may appear postoperatively, if not present before. For this reason a new operation was devised, consisting in the removal of the exostosis, removal of the cartilage from the proximal end of the phalanx and removal of all of the phalanx except the very base containing the attachments of the adductor hallucis muscles. This small block of bone is fastened as far medial as possible on the head of the first metatarsal bone with a beef bone peg. This operation improves or prevents splayfoot as well as relieves the hallux valgus and hallux rigidus. Ten of 20 patients with hallux valgus treated by subtotal phalangectomy complained of metatarsalgia and splayfoot postoperatively and 3 complained of them preoperatively. Thirteen of 30 patients who were operated on by the new technic had metatarsalgia preoperatively, but only 1 complained of it postoperatively.

FRACTURES

Metge[30] describes an avulsion fracture of the spinous process which occurs while the patient is working. Detachment of the spinous process of the seventh cervical vertebra is the most common form; less commonly the first or second dorsal spinous processes are involved. The lesion occurs when a workman bends his head backward while he is hurling a heavy shovelful of earth upward onto a truck. It has long been described as a clinical syndrome which is often incorrectly diagnosed. Roentgenographic study reveals the lesion if the plates are properly exposed with the lesion in mind. The author finds that excision of the avulsed spinous process results in the quickest and surest recovery.

Anomalies and Fractures of the Vertebral Articular Processes.—Bailey[31] describes and differentiates between anomalous fissures across the vertebral articular processes and fractures in this region. Anomalous centers of ossification at the tips of the articular processes are more frequent than commonly supposed. In half the 10 cases described the history of trauma was vague or entirely absent. The defect was often bilateral, and rarely were the superior processes affected. Fracture of the articular process without other injuries to the spine was rare. Pain was prompt and severe, and the fragments were usually displaced.

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[29] Girdlestone, R. G., and Spooner, H. J.: J. Bone & Joint Surg. **19**:30, 1937.

[30] Metge, E.: Deutsche med. Wchnschr. **62**:1922 (Nov. 20) 1936.

[31] Bailey, W.: Anomalies and Fractures of Vertebral Articular Processes, J. A. M. A. **108**:266 (Jan. 23) 1937.

Ununited Fractures of the Shaft of the Humerus.—The end-results in any large series of ununited fractures treated by operative methods are rarely reported. Campbell[32] reports the end-results in 50 cases of ununited fracture of the shaft of the humerus. One patient with an oblique fracture line was treated by transfixion of the fragments with autogenous bone pegs, solid union resulting. The remaining 49 were treated by the application of a massive onlay graft from the tibia secured by autogenous bone pegs. In addition to this, a strip of endosteum was placed within the medulla and bony shavings were placed about the site of the fracture. There were 3 failures in the 49 patients so treated. There were no failures in the 4 patients in whom postoperative infection occurred.

[ED. NOTE.—The results in this series of cases are excellent. The high percentage of successful unions would indicate that this is the method of choice in treating nonunion of the shaft of the humerus and that less secure means of fixation should be discarded.]

Results of Fractures of the Olecranon.—Laukka[33] treated 103 fractures of the olecranon and was able to study the end-results in 56 cases. Five fractures were compound. Loose fragments in the elbow joint were seen in 17 patients. Thirty-five patients were treated by immobilization alone. This was used chiefly in children in whom there was separation of not more than 5 mm. and nothing prevented complete apposition of the fragments. Sixty-five patients were operated on. In most cases stainless steel wire was used to hold the fragments together, and in a few cases, silk. In the follow-up study 10 of 11 patients were found to have less than 20 degrees limitation of motion. Good function was seen in all of these patients. Less than 20 degrees limitation of motion was seen in 22 of 33 patients. Pseudarthrosis was found in 6 patients. Arthritis deformans was frequently seen one or two years after the fracture in 36 per cent of those operated on and in 13 per cent of those treated conservatively. Fracture of the head of the radius was a complication in 7 patients.

Fractures of the Neck of the Femur.—Magnuson[34] attempted to evaluate the various methods of treatment used for fracture of the neck of the femur. A fracture in this region should be classified according to its line and plane and according to the amount of displacement which originally occurred. When there is considerable obliquity of the fracture line, visual reduction is preferable with immediate fixation. Each patient presents an individual problem. While the Whitman, the Leadbetter and the well leg traction method have their place, internal fixation of the fragments gives greater comfort and makes nursing care easier and the chances of union greater. The author feels that close bony contact, anatomic apposition and absolute fixation are the three most important factors in securing union.

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[32] Campbell, W. C.: Ann. Surg. **105**:135, 1937.

[33] Laukka, E.: Acta chir. Scandinav. **79**:93, 1936.

[34] Magnuson, P. B.: Fracture of Neck of Femur: Evaluation of Various Methods Advanced for Treatment, J. A. M. A. **107**:1439 (Oct. 31) 1936.

"March Foot."—Elward[35] reviews the literature on "March foot" due to foot strain and fracture of a metatarsal bone. He describes two varieties, one due to sudden strain of the foot with fracture of a metatarsal bone and the other due to chronic foot strain and fracture of a metatarsal bone with no definite history of trauma. In the roentgenograms one must differentiate chiefly between sarcoma and Köhler's disease. In the absence of trauma, sarcoma may be suspected, but roentgenograms do not show the "sun-ray" structure. In cases in which the diagnosis is doubtful, weekly roentgenographic examination should make the diagnosis clear. Conservative treatment is indicated.

Fractures of the Neck of the Femur in Childhood.—Mitchell[36] reports 10 cases of fracture of the neck of the femur in children. He divides the lesion into three types: (1) epiphysial separation, (2) transcervical fracture and (3) cervicotrochanteric fracture. Bony union practically always occurs, often with coxa vara. The author advises treatment by continuous traction with the hip immobilized in abduction.

Traumatic Separation of the Upper Femoral Epiphysis.—Pfeiffer[37] adds 3 cases to the list of cases of traumatic separation of the upper femoral epiphyses during childbirth. The lesion is not easy to recognize. Crepitus is usually absent. Swelling or limitation of motion of the hip generally calls attention to the injury. Careful roentgenographic study will reveal displacement of the intact shaft early and bony callus later. Early recognition, replacement and adequately long fixation are essential if traumatic coxa vara is to be avoided.

Fractures in the New-Born.—A review of the last 6,000 cases of fracture at the Boston Children's Hospital reveals 115 birth fractures, 34 per cent of which were not recognized at the time of their occurrence. In this series the fractures were distributed as follows: fracture of the clavicle, 53; of the humerus, 38; of the femur, 20, and of the tibia, 4, including 3 of the fibula also. Unusual obstetric maneuvers were required for 20 per cent of the fractured clavicles, 92 per cent of the fractured humeri, 72 per cent of the fractured femurs and 50 per cent of the fractured tibias. Thorndike and Pierce[38] believe that adequate treatment of fractures in the new-born should consist in: (1) early diagnosis, (2) prompt realinement of the fragments (healing is so rapid that after five days it is impossible to reduce the fractures manually), and (3) proper fixation until union has taken place. Methods of treatment are explained in this article: A skein of yarn with figure eight traction is recommended for a fractured clavicle. It was found that in 100 per cent of the cases in which fracture of the femur was treated by strapping the femur to the abdomen the result was unsatisfactory; for this reason an overhead frame with adhesive traction is recommended. Not one instance of true intra-uterine fracture was found in this review. In most cases in this series the fracture occurred in a large baby.

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[35] Elward, J. F.: Am. J. Roentgenol. **36**:188, 1936.

[36] Mitchell, J. I.: Fracture of Neck of Femur in Children, J. A. M. A. **107**: 1603 (Nov. 14) 1936.

[37] Pfeiffer, R.: Beitr. z. klin. Chir. **164**:18, 1936.

Injection of Alcohol into the Intercostal Nerve in Treatment of Fractures of the Ribs.—Rabboni[39] reports 10 cases of fracture of the ribs in which the therapeutic method of Latteri was used. Rabboni states that external splinting does not suffice to immobilize a fractured rib sufficiently to relieve pain and allow normal respiratory movements. If a small amount of alcohol is injected in the vicinity of the corresponding intercostal nerves, nerve block ensues. This is accompanied by complete relief of pain, normal respiration and, without splinting, normal healing of the fractures. If injection into more than two nerves is necessary, the nerves are taken in couples on consecutive days. The procedure of injection consists of inserting the needle at right angles to the undersurface of the rib, and with the needle in contact with the rib it is gently manipulated so that the point is upward just mesial to the inferior ridge of the rib.

[Ed. Note.—This method of treatment should be used with caution. Unfortunate complications have followed failure to splint broken ribs. Injection into the intercostal nerve is also not without danger.]

Procaine Hydrochloride in the Treatment of Articular Fractures.—In cases of fracture in which there is little or no displacement and in which maintenance of position with apparatus is unnecessary, Leriche and Froehlich[40] have been starting active motion of the adjacent joint immediately. They first inject 1 per cent procaine hydrochloride into the soft tissues about the fracture and if possible into the fracture fissure itself. The effect of this injection lasts for from twelve to twenty-four hours, and the treatment is repeated daily for from two to three weeks. Active motions are repeatedly performed while the parts are under the anesthesia. The authors believe that restoration of function is greatly hastened by this method. In 2 of the reported cases there was gross displacement of the radial head. No attempt was made to reduce or remove the head, but excellent function was obtained in each case by the method described.

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[38] Thorndike, A., and Pierce, F. R.: New England J. Med. **215**:1013 (Nov. 26) 1936.

[39] Rabboni, F.: Chir. d. org. di movimento **22**:263, 1936.

[40] Leriche, R., and Froehlich, F.: Presse méd. **44**:1665 (Oct. 24) 1936.

[Ed. Note.—Fracture without displacement and needing no fixation usually gives little trouble however treated. *In the foregoing cases of* fracture of the head of the radius, both marked displacement and restoration of function without removal of the head seem extraordinary. It does not seem likely that such results could be obtained uniformly.]

RESEARCH

Studies in Healing of Fractures.—Krull[41] studied the problem of healing of fractures with cultures of tissue from chick embryos. At ten days the anlage of the femur was freed from the surrounding tissue. The femur was twisted, and the broken pieces were placed in dishes or flasks containing a mixture of chicken plasma and embryonal extract. Different mineral concentrations and temperatures were investigated. While fibroblastic repair was seen, no calcification or bone production occurred.

Thymus and Bone Regeneration.—Portions of the radius were resected by Haas and Hanke[42] in rabbits, and healing was observed in a group of animals from which the thymus had been removed. This group did not show any essential difference in bone formation from the control group. The feeding of thymus extract to the animals after the removal of the thymus had no effect either. The rabbits chosen were all growing young animals.

Thyroid Activity and Healing of Fractures.—Eitel and Lexer[43] administered thyroid preparations to rabbits. After fracture of the humerus, administration of thyroid was continued, and at various dates the rabbits were anesthetized and mercury was injected into the axillary artery of the fractured extremity. Study of the visualized blood supply of the sites of the fractures indicated that the administration of thyroid caused hyperemia in the area of the callus to occur earlier and that the callus was stronger and lasted longer than in the control animals.

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41. Krull, G.: Arch. f. orthop. u. Unfall-Chir. **37**:131, 1936.
42. Haas, A., and Hanke, H.: Deutsche Ztschr. f. Chir. **247**:724, 1936.
43. Eitel, H., and Lexer, E. W.: Arch. f. klin. Chir. **185**:587, 1936.

Influence of the Mineral Constituents of Bone on Ossification.—As a result of carefully controlled animal experimentation, Bisgard[44] concludes that the synthetic bone salts calcium carbonate, calcium phosphate and magnesium phosphate when locally deposited had no influence on osteogenesis or ossification, whereas bone in the form of partially viable bone, boiled bone or bone ash had a favorable influence on ossification when deposited locally.

Metastases from Tumor Transplants.—Schopper[45] reports the results of studies on osseous metastases from tumor material injected intravenously into rabbits. The Brown-Pearce[46] rabbit tumor was used. The rabbits were killed at varying intervals. The metastatic tumors showed best in from three to four weeks. Proliferating tumors were found often as foci without any marked reaction in the surrounding tissue; sometimes there was destruction of bone; rarely was there new bone formation. Tumors were found in the bone marrow and under the periosteum, chiefly in the region of the metaphyses of the long bones. The periosteal tumors were primary transplants and not extensions from the marrow cavity. They stimulated osteophytic activity and at the same time destroyed bone by pressure. New bone formation occurred chiefly by laying down layers of new bone. Rarely was there a metaplasia of the surrounding stroma. No deformities or pathologic fractures were observed.

Study of the Supraspinatus Tendon in Cadavers.—Skinner,[47] on the basis of dissections on cadavers, presents a description of changes occurring in the supraspinatus tendon in response to continued trauma and to age. It would appear that about 20 per cent of all adult shoulders show some degree of change in the supraspinatus tendon, of which one fourth will show some degree of rupture or splitting. Because of its anatomic relations, the supraspinatus tendon is subject to changes consisting of alteration from fleshy fibers ending in a short tendon to a wide aponeurosis of fibrous tissue blending with the infraspinatous tendon. When this has occurred, because of weakness, splitting, rupture or calcification may follow. Associated changes occur in the greater tuberosity, the intertubercular sulcus, the articular cartilage and the tendon of the long head of the biceps muscle.

Vascularization and Pathologic Structure of the Cotyloid Ligament.—An excellent study of the circulation of the acetabulum is given by Logroscino and Dotti.[48] The blood supply is derived from the superior and the inferior gluteal vessels and from the obturator. Because of the blood supply, localization or infectious lesions and trophic changes following trauma may be explained.

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[44] Bisgard, J. D.: Ossification: Influence of Mineral Constituents of Bone, Arch. Surg. **33**:926 (Dec.) 1936.

[45] Schopper, W.: Virchows Arch. f. path. Anat. **298**::527, 1937.

[46] Domagk, G.: Centralbl. f. allg. Path. u. path. Anat. **61**:108, 1934.

[47] Skinner, H. A.: J. Bone & Joint Surg. **19**:137, 1937.

[48] Logroscino, D., and Dotti, E.: Chir. d. org. di movimento **22**:285, 1936

[Ed. Note.—This article is too long and full of data to abstract, but it merits reading by all interested in the anatomic and pathologic structure of the acetabulum.]

Ligamentum Teres and Its Vessels.—Schwaiger[49] studied the ligamentum teres femoris grossly and microscopically at various age periods. He found that vessels could be found in the ligamentum teres up to old age. From the age of 2 years upward there was progressive obliteration of the blood vessels. He believes that the importance of the vessels in the ligamentum teres has been overestimated. No pathologic changes were observed in the cartilage of the upper end of the femur or the surrounding tissues from obliteration of the vessels in the ligamentum teres.

Correlation of Pathologic and Roentgenographic Findings in Tuberculous and Pyogenic Infection of the Vertebrae.—Various authors have assumed that tuberculous or pyogenic hematogenous infection may localize first in the intervertebral disk. Compere and Garrison[50] point out the fact that the adult intervertebral disk has no blood supply and therefore the disk is never the site of primary infection but is affected by secondary invasion from some adjacent vertebral focus. In a pathologic study of 4 cases of uncomplicated Pott's disease they found that the primary focus was in the vertebral body, either in the centrum or near the epiphysial ring. The disk tissue acted in similar fashion to articular cartilage in other joints and was resistant to destruction. The disease spread by extension beneath the longitudinal ligament and not directly through the disks. The narrowing of the intervertebral space commonly noted seemed to be due to extrusion of the nucleus pulposus through a weakened annulus fibrosus or cartilage plate. In two cases of pyogenic osteomyelitis pathologic examination showed rapid destruction of the adjacent intervertebral disk, as joint cartilage is rapidly destroyed by the proteolytic enzymes in the pyogenic exudate. In contrast to tuberculous infection, regeneration of bone and ankylosis of the vertebral bodies are much more likely to occur in pyogenic infection. The results of microscopic examination in 3 cases of mixed infection (tuberculous plus pyogenic) of the spine were reported.

Rôle of the Reticulo-Endothelial System in the Deposition of Colloidal Matter in Articular Cavities.—In studying the rôle of the reticulo-endothelial system in the deposition of colloids and particulate matter in articular cavities, Kuhns and Weatherford[51] used rats into which they injected trypan blue subcutaneously or by gavage. Various series of experiments were made in an attempt to exclude the rôle of the lymphatics. In conclusion, the authors found that colloidal and particulate matter was carried to the articular cavities from the various tissues of the body, such as the skin and the gastro-intestinal tract, through the blood stream. This material was stored chiefly in histiocytes in the synovial membrane, in the bone marrow and in lesser amounts in the intermuscular septums and in the articular fat pads. Mild inflammation in articular tissues tended to increase the amount of deposition of such transplanted substances. Local blocking of the reticulo-endothelial system was transitory and incomplete and was not effective in preventing the deposition of colloidal and particulate matter in articular tissue.

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[49] Schwaiger, M.: Ztschr. f. Orthop. **65**:297, 1936.

[50] Compere, E. L., and Garrison, M.: Ann. Surg. **104**:1038, 1936.

Auscultation of Joints.—Steindler[52] stresses the importance of auscultation in the examination of joints. He presents a preliminary report based on the auscultatory findings in a series of 397 knee joints. The instruments used were the stethoscope, the cardiaphone and the oscillograph. The interpretation of sound phenomena is difficult because extraneous and extra-articular noises must be differentiated from the intra-articular noises. However, certain sounds can be considered intra-articular because of their character and the regularity of their occurrence. Sustained grating in all quadrants of the knee joint indicates general involvement of the joint with arthritic changes which may or may not be the background of isolated internal derangements. Isolated sounds are cracks, clicks and thuds. High-pitched cracks indicate a hard body, such as a joint mouse, while lower-pitched clicks and thuds indicate softer bodies, such as fringes and semilunar cartilages. The author does not claim to be able to make definite diagnosis by auscultation but feels that it is of aid in locating the lesion inside the joint.

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[51] Kuhns, J. G., and Weatherford, H.: Rôle of Reticulo-Endothelial System in Deposition of Colloidal and Particulate Matter in Articular Cavities, Arch. Surg. **33**:69 (July) 1936.

[52] Steindler, A.: J. Bone & Joint Surg. **19**:121, 1937.

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INCIDENCE OF ASYMPTOMATIC PATHOLOGIC CONDITIONS OF THE APPENDIX

BASED ON A STUDY OF 2,065 CONSECUTIVE INCIDENTAL APPENDECTOMIES

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This paper is based on a study of the records of 2,065 consecutive incidental appendectomies performed at St. Luke's Hospital in the period between 1925 and 1935 inclusive. The word incidental as used here refers to those appendectomies performed during abdominal operations, the indications for which were in no way associated with the appendix. None is included which was performed when present or past disease of the appendix was suspected before operation. Doubtless some of the patients may have had appendical symptoms at some time in the past, but neither the history nor the physical findings suggested any pathologic condition of the appendix.

Originally this analysis was undertaken to obtain a standard for comparison with the pathologic conditions found in appendixes removed because of symptoms attributed to chronic appendicitis. By selecting the material as previously noted and then eliminating all in which any inflammatory condition was present elsewhere in the abdomen, the resultant figures should approximate closely the expected incidence of pathologic changes in the appendix when it is not the cause of the patient's symptoms. In obtaining the set of figures just described, other statistics were obtained which appeared to be of considerable interest. This paper was written to present these figures.

So far as possible, everything was excluded which pertained to the primary operation, and attention was centered on the results of the study of the appendixes. In order to do this, the incidences were calculated on the total number of appendixes in each group under consideration at the time and not on the total number in the whole series. In this way comparisons have been made in which the effect of the indications for the primary operations were largely, if not entirely, eliminated.

Presented before the New York Academy of Medicine, Section of Surgery, Dec. 4, 1936.

REGION OF THE PRIMARY OPERATION

The data in table 1 are given only to show how the primary operations were distributed in regard to the operative region. A detailed list of the operations was felt to be too complicated, particularly as from 2 to 6 different operative procedures other than appendectomy were performed on many of the patients. There is an apparent increase of 110 operations over the total of 2,065, because in some instances the primary operative procedures were done on the same patient in two different regions. Additional operative procedures outside of the abdomen, of which there were a considerable number, were not listed.

The mortality for each group did not appear to be above the normal expectancy, with but one exception. This was for the operations performed for some condition associated with the colon. A careful study of this material and of the causes of death shows that the mortality was not above the normal expectancy, although this does not obviate the fact that it was unwise to add an appendectomy to the primary operation, which was imperative.

TABLE 1.—*Distribution of Primary Operations According to the Operative Region, With Mortality for Each Group* *

Operative Region	Number of Operations	Number of Deaths	Mortality, Percentage
Female generative organs	1,654	13	0.79
Gallbladder and liver	312	5	1.61
Hernia	68	0	0.00
Stomach and duodenum	53	2	3.77
Colon	17	5	29.82
Small intestine	6	0	0.00
Other intra-abdominal regions	65	2	3.07

* The total number of primary operations is increased to 2,175 because often a "primary" operation was done in more than one region on the same patient. When more than one operative procedure was performed in one region they are listed as one operation. Additional operative procedures not involving the abdominal cavity are not listed.

INCIDENCE OF PATHOLOGIC CONDITIONS IN THE APPENDIX

Table 2 lists the pathologic conditions in the appendixes, their incidence (calculated on 1,904 examined microscopically) and the mortality for each group.

No microscopic examination was made of 161 appendixes. Of those examined, 14 showed conditions other than a nonspecific inflammation. These, together with 7 which showed some pathologic process in addition to a nonspecific inflammation, will be considered in tables 13 and 14. The latter 7 are also listed in their proper place according to the inflammatory change.

This leaves 1,890 appendixes which formed the basis for the figures in tables 3 to 12 and in charts 1 to 16. A brief definition of the various types of inflammatory change is given. They have been listed separately throughout the tables, as it was felt that the term chronic appendicitis was too ambiguous.

No Definite Evidence of Inflammation.—In 702 appendixes no definite evidence of inflammation was found. These made up 37 per cent of the group now being discussed. They were divided pathologically into the two classes listed here.

Normal Appendixes: All appendixes which appeared normal or relatively normal with no definite pathologic change were listed as normal. There were 629 appendixes, or 33 per cent of the total, in this group.

Atrophic Appendixes: The wall of an atrophic appendix is very thin and shows no definite evidence of inflammation. This condition is due largely to pressure from within the appendix, present over an appreciable period of time. Seventy-three appendixes, 4 per cent of the total, showed this pathologic change.

Definite Inflammatory Changes.—As contrasted to the appendixes with no definite evidence of inflammation, 1,188, or 62 per cent of the 1,890 being discussed, showed definite inflammatory change. These have been divided into two main groups according to the degree of the inflammatory change present.

Simple Chronic Appendicitis: In this group were placed those appendixes showing a definite, but not marked, evidence of chronic inflammation throughout the various parts of the wall or only in the mucosa and submucosa. This lesion was found in 573 appendixes, or 48 per cent of those showing inflammatory change (30 per cent of the total group).

Marked Inflammatory Changes: As contrasted to the foregoing group, a more extensive inflammatory lesion was found in 615 appendixes, or 52 per cent of those showing inflammatory change (32 per cent of the total group). The various types of conditions which this included will be discussed.

Chronic catarrhal appendicitis is characterized by a moderate degree of chronic inflammation in the mucosa and submucosa, with definite catarrhal changes in the mucosa and usually a slight infiltration in the muscle. This lesion was found in 82 appendixes, or 13 per cent of those showing marked changes (4 per cent of the total group).

Chronic exudative appendicitis is a definite pathologic lesion which is often seen as a late stage in the recovery from an attack of acute appendicitis. It is characterized, as the name indicates, by a marked chronic exudative process. There is a dense extensive infiltration with the various cells typical of chronic inflammation, and often chronic edema is present. The lumen of the appendix, the blood vessels and the perivascular tissues frequently contain some polymorphonuclear leukocytes. This lesion was found in 157 appendixes, or 26 per cent of those showing marked changes (8 per cent of the total group).

Acute appendicitis, which requires no definition, was found in 33 appendixes, or 5.4 per cent of those which showed marked changes (2 per cent of the total group). An acute suppurative process was present in 6, an acute and acute catarrhal process in 12 and a subacute process in 15. The subacute process lies between acute and chronic exudative appendicitis.

The records of the patients from whom the foregoing 33 appendixes were removed were rechecked for any history or physical findings which would even suggest the possibility of appendical disease at the time of the operation or previously. None could be found. Three of the acute suppurative appendixes were removed from my own personal patients. In each instance, after the pathologic changes were reported the history was rechecked with the patient. No overlooked points in the history which pointed in any way to the presence of appendicitis were disclosed.

One must bear in mind the possibility that the pathologic changes present in some of the appendixes which presented acute or subacute, but not suppurative, inflammation might have been produced by the appendix having been packed away tightly with pads while a long primary operation was being performed.

Chronic obliterative appendicitis with infiltration likewise requires no definition, as the name gives a complete description of the pathologic lesion. The mucosa and often the other coats, even including a part of the muscle, have disappeared and been replaced by granulations or scar tissue, which, with the muscle, shows a definite infiltration. The process may involve a part of or the whole appendix. It probably represents either a stage in the healing of a suppurative or ulcerative process or a renewed inflammation in an appendix which had previously healed. This condition was observed in 106 appendixes, or 17 per cent of those showing marked changes (6 per cent of the whole group).

Chronic obliterative appendicitis without infiltration is, as the name designates, the same as the foregoing condition with the exception that it is a completely healed process without inflammation. One hundred and eighty-three appendixes were so effected, or 30 per cent of those showing marked pathologic changes (10 per cent of the total group). Of the 7 groups of appendixes which presented marked inflammatory changes, this was the largest.

Chronic periappendicitis is associated with and due to a chronic inflammatory lesion elsewhere in the abdomen, usually chronic salpingitis. This pathologic condition was present in 31 appendixes, or only 5 per cent of those showing marked changes (2 per cent of the total group). The number was surprisingly small considering the large number of cases of salpingitis included in the list.

Acute periappendicitis constitutes its own definition. This condition is associated with and due to an acute inflammatory lesion elsewhere in the abdomen. It was found in only 23 appendixes, or 3.7 per cent of those which showed marked changes (1 per cent of the total group). This group was small because ordinarily the primary lesion in the abdomen and the patient's condition were contraindications to doing an incidental appendectomy.

MORTALITY ACCORDING TO CONDITION FOUND IN THE APPENDIX

The mortality figures are given only for completeness. The pathologic condition found in these appendixes had no bearing on any of the deaths in this list. Any increase above the average is due to the primary operation or to the indication for that operation.

Table 2.—*Classification of Pathologic Conditions of Appendixes, With the Incidence and Mortality for Each Group*

Condition in Appendix	Number of Appendixes	Percentage*	Number of Deaths	Mortality, Percentage
No microscopic examination	161	....	1	0.62
Mucocele	3	0.16	0	0.00
Tuberculosis	5	0.26	1	20.00
Tumor	6	0.32	0	0.00
No inflammation	702	36.9	5	0.71
Normal 629		33.1	4	0.62
Atrophic 73		3.8	1	1.37
Inflammation	1,188	62.4	20	1.67
Simple chronic appendicitis 573		30.1	10	1.75
Marked inflammatory changes 615		32.3	10	1.63
Chronic catarrhal appendicitis 82		4.3	1	1.22
Chronic exudative appendicitis 157		8.3	2	1.27
Acute appendicitis 33		1.7	0	0.00
Chronic obliterative appendicitis with infiltration 106		5.6	1	0.94
Chronic obliterative appendicitis without infiltration 183		9.6	4	2.19
Chronic periappendicitis 31		1.6	0	0.00
Acute periappendicitis 23		1.2	2	8.70
Totals	2,065	100.00	27	1.31

* The percentages are calculated only on the 1,904 appendixes examined microscopically.

The number of tuberculous appendixes was too small for the mortality percentage to be significant. The single death was due to generalized tuberculosis.

Chronic obliterative appendicitis with infiltration is found to a large extent in older patients. They are poorer operative risks and more often require extensive primary operations for more serious conditions than younger patients. Possibly this argues that they should not undergo an incidental appendectomy, although the mortality for the group reported here is no greater than would be expected had the appendectomy not been done.

The increase in mortality in the group of patients with acute periappendicitis was caused by the death of 2 with advanced generalized peritonitis due to a perforated diverticulum of the sigmoid colon. Undoubtedly these patients should not have been subjected to an appendectomy.

RELATION OF INFLAMMATORY CHANGE IN THE APPENDIX TO INFLAMMATION ELSEWHERE IN THE ABDOMEN

The relationship of inflammatory change in the appendix to inflammation elsewhere in the abdomen, without taking into consideration the type or location of the latter, is shown in table 3. This and all subsequent percentage charts have been so arranged that comparisons may be made by reading down the columns of percentages. Any effect that the items listed on the left had on the items listed at the top of the table are shown by variations in the vertical columns of figures.

Table 3.—*Relation of the Inflammatory Change in the Appendix to the Incidence of Inflammation Elsewhere in the Abdomen* *

Condition in Appendix			Total Appendixes	Condition Elsewhere in Abdomen			
				No Inflammation		Inflammation	
				Number	Percentage	Number	Percentage
No inflammation			702	465	66.2	237	33.8
Normal		629		415	66.0	214	34.0
Atrophic		73		50	68.5	23	31.5
Inflammation			1,188	674	56.8	514	43.2
Simple chronic appendicitis		573		320	55.8	253	44.2
Marked inflammatory changes		570		354	62.1	216	37.9
Chronic catarrhal appendicitis	82			55	67.0	27	33.0
Chronic exudative appendicitis	157			94	59.8	63	40.2
Acute appendicitis	33			23	69.7	10	30.3
Chronic obliterative appendicitis with infiltration	106			59	55.7	47	44.3
Chronic obliterative appendicitis without infiltration	183			119	65.0	64	35.0
Chronic periappendicitis	31			4	12.9	27	87.1
Acute periappendicitis	23			0	00.0	23	100.0
Totals			1,890	1,139	60.3	751	39.7

* For comparisons read the vertical percentage columns. This table is elaborated in tables 4 and 5.

The distribution of the appendixes according to the various types and locations of inflammation elsewhere in the abdomen is presented in table 4, and the corresponding incidences, figured on the total number of appendixes listed under each type of pathologic condition found elsewhere in the abdomen, in table 5. A slight increase in the incidence of appendixes showing inflammatory change accompanied the presence of inflammation elsewhere in the abdomen. This increase was greatest in the groups of appendixes affected with periappendicitis. Here, of course, the cause of this increase was elsewhere than in the appendix, and the relation is self-evident.

No cases of acute appendicitis were included under the headings chronic suppurative and acute salpingitis. In looking up the records, 30

TABLE 4.—*Distribution of Appendixes According to the Various Types of Inflammation Occurring Simultaneously Elsewhere in the Abdomen*

Condition in Appendix	Condition Elsewhere in Abdomen: No Inflammation	Inflammation	Salpingitis	Chronic Salpingitis	Chronic Suppurative Salpingitis	Acute Salpingitis	Cholecystitis	Peptic Ulcer	Tuberculous Peritonitis or Salpingitis	Peritonitis	Other Types of Inflammation	Total Appendixes
No inflammation	465	237	145	125	9	11	74	13	3	1	1	702
Normal	415	214	135	115	9	11	63	12	2	1	1	629
Atrophic	50	23	10	10	0	0	11	1	1	0	0	73
Inflammation	674	514	306	202	50	51	161	29	5	6	7	1,188
Simple chronic appendicitis	320	253	118	105	30	13	80	13	5	3	4	573
Marked inflammatory changes	354	261	158	97	20	11	81	16	0	3	3	615
Chronic catarrhal appendicitis	55	27	20	16	1	3	7	0	0	0	0	82
Chronic exudative appendicitis	94	63	39	27	2	10	18	5	0	0	1	157
Acute appendicitis	23	10	2	2	0	0	7	0	0	1	0	33
Chronic obliterative appendicitis with infiltration	59	47	19	13	2	4	19	7	0	0	2	106
Chronic obliterative appendicitis without infiltration	119	64	30	25	2	3	30	4	0	0	0	183
Chronic periappendicitis	4	27	27	13	13	1	0	0	0	0	0	31
Acute periappendicitis	0	23	21	1	0	20	0	0	0	2	0	23
Totals	1,139	751	451	327	59	65	235	42	8	7	8	1,890

TABLE 5.—*Distribution of Appendixes According to Various Types of Inflammation Occurring Simultaneously Elsewhere in the Abdomen (Percentages)* *

Condition in Appendix	Total Appendixes	Condition Elsewhere in Abdomen										
		No Inflammation	Inflammation	Salpingitis	Chronic Salpingitis	Chronic Suppurative Salpingitis	Acute Salpingitis	Cholecystitis	Peptic Ulcer	Tuberculous Peritonitis or Salpingitis	Peritonitis	Other Types of Inflammation
No inflammation	702	66.24	33.76	20.65	17.81	1.28	1.56	10.45	1.85	0.44	0.14	0.14
Normal	629	65.97	34.03	21.46	18.28	1.43	1.75	10.02	1.91	0.32	0.16	0.16
Atrophic	73	68.49	31.51	13.69	13.69	0.00	0.00	15.07	1.37	1.37	0.00	0.00
Inflammation	1,188	56.73	43.27	25.76	17.00	4.21	4.55	13.55	2.44	0.43	0.50	0.59
Simple chronic appendicitis	573	55.85	44.15	25.83	18.32	5.23	2.27	13.96	2.27	0.87	0.52	0.70
Marked inflammatory changes	615	57.56	42.44	25.76	15.77	3.25	6.67	13.17	2.60	0.00	0.49	0.49
Chronic catarrhal appendicitis	82	67.07	32.93	24.39	19.51	1.22	3.66	8.54	0.00	0.00	0.00	0.00
Chronic exudative appendicitis	157	59.87	40.13	24.83	17.19	1.27	6.37	11.47	3.19	0.00	0.00	0.64
Acute appendicitis	33	69.70	30.30	6.06	6.06	0.00	0.00	21.21	0.00	0.00	3.03	0.00
Chronic obliterative appendicitis with infiltration	106	55.66	44.34	17.92	12.26	1.89	3.77	17.92	6.61	0.00	0.00	1.89
Chronic obliterative appendicitis without infiltration	183	65.03	34.97	16.30	13.66	1.09	1.64	16.39	2.19	0.00	0.00	0.00
Chronic periappendicitis	31	12.90	87.09	87.09	41.93	41.93	3.23	0.00	0.00	0.00	0.00	0.00
Acute periappendicitis	23	0.00	100.00	91.30	4.35	0.00	86.96	0.00	0.00	0.00	8.70	0.00
Figures for whole group	1,890	60.26	39.74	23.86	17.30	3.12	3.44	12.43	2.22	0.43	0.37	0.43

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* The percentage incidence was calculated on the total number of appendixes classified with each type of pathologic condition found elsewhere in the abdomen. For comparisons, read the vertical columns.

cases were found in which subacute, acute or acute suppurative appendicitis occurred simultaneously with one of these two conditions when the indication for the operation was a pathologic condition of the tubes. However, they were all discarded as it was impossible to state positively that the symptoms were not at least partially due to the inflammatory process in the appendix.

One portion of this table is interesting because of the definite lack of relationship shown and will be taken up in detail later.

RELATION OF INFLAMMATORY CHANGE IN THE APPENDIX TO INFLAMMATION IN THE GALLBLADDER

The statement has often been made that inflammation in the gallbladder is largely, or at least frequently, caused by a chronic inflammatory process in the appendix. Tables 6 and 7 and charts 1 and 2 present the statistics for cases in which the gallbladder and appendix were removed simultaneously. If inflammation in the appendix causes inflammation in the gallbladder, the incidence of cholecystitis should show a definite increase when inflammation is found in the appendix, and one might expect that increase to be greater the more marked the inflammatory change in the appendix. The tables and charts do not show this. In fact, there is a slight variation in the opposite direction (table 6 and chart 1). Conversely, the incidence of normal gallbladders should be decreased in the presence of inflammatory change in the appendix. As before, a slight variation in the opposite direction is found (table 6 and chart 2).

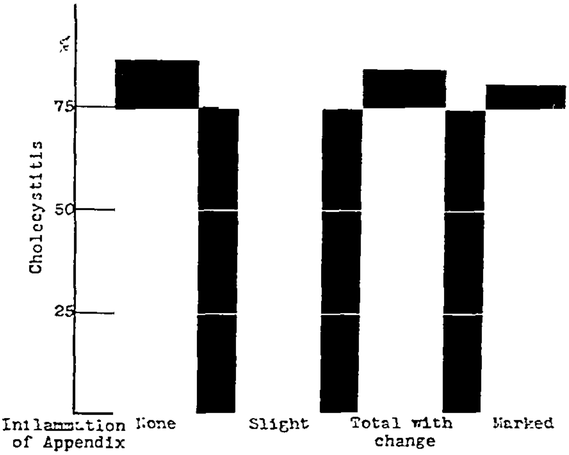

Chart 1.—Relation of inflammatory change in the appendix to the incidence of inflammation in the gallbladder. The incidence of the latter does not increase in the presence of inflammatory change in the appendix.

The same relation is presented in table 7, but the incidence of inflammatory change in the appendix was calculated on the number of normal gallbladders and those showing cholecystitis. The same lack of causative relationship is seen.

A careful examination of these figures discloses no evidence to substantiate the statement that chronic inflammation in the appendix causes inflammation in the gallbladder.

TABLE 6.—*Relation of Inflammatory Change in the Appendix to Inflammation in the Gallbladder* *

		Condition in Gallbladder			
		Normal		Cholecystitis	
Condition in Appendix	Total Appendixes	Number	Percentage	Number	Percentage
No inflammation	86	12	13.9	74	86.1
Inflammation	190	29	15.3	161	84.7
Slight	90	10	11.1	80	88.9
Marked	100	19	19.0	81	81.0
Totals	276	41	14.8	235	85.2

* This table indicates that inflammation in the appendix is not a cause of inflammation in the gallbladder. If it were, an increase in the incidence of cholecystitis should be found in the presence of inflammatory change in the appendix. There is instead a slight decrease in incidence. This table is shown graphically in charts 1 and 2.

TABLE 7.—*Relation of Inflammation in the Gallbladder to Inflammatory Change in the Appendix* *

		Inflammatory Change in Appendix							
		None		Total		Slight		Marked	
Condition in Gallbladder	Total Cases	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Normal	41	12	29.1	29	70.9	10	24.4	19	46.5
Cholecystitis	235	74	31.5	161	68.5	80	34.2	81	34.3
Totals	276	86	31.1	190	68.9	90	32.6	100	36.4

* This table indicates that in the presence of inflammation in the gallbladder there is no increase in the incidence of inflammatory change in the appendix.

RELATION OF INFLAMMATION ELSEWHERE IN THE ABDOMEN TO INFLAMMATORY CHANGE IN THE APPENDIX

The distribution of inflammatory conditions in the abdomen and their proportionate frequency, without taking into consideration the type of inflammatory change in the appendix, is presented in table 8. The distribution is shown in detail in table 9, and the corresponding incidences, calculated on the total number of cases in each group, in table 10.

By reading down the percentage columns in table 10 under each type of pathologic process found in the appendix, the effect, if any, on each pathologic process of inflammation elsewhere in the abdomen can be readily seen. An extensive discussion is unnecessary.

In the presence of inflammation elsewhere in the abdomen there was a definite increase in the incidence of inflammatory change in the appendix. This same relation held true with simple chronic appendicitis, marked inflammatory changes (total), chronic obliterative appendicitis with infiltration and, as one would expect, to a much greater extent with chronic and acute periappendicitis. No causative relationship was indicated in chronic catarrhal appendicitis, chronic exudative appendicitis, acute appendicitis and chronic obliterative appendicitis without infiltration. Apparently inflammation elsewhere in the abdomen has no appreciable effect on any of the latter group of changes found in the appendix. The only really outstanding relationship shown was that of salpingitis and peritonitis in causing acute and chronic periappendicitis.

What appears to be an abnormal variation under chronic obliterative appendicitis (both groups) was due to what is later shown to be age incidence. Here the higher percentages were found in those conditions occurring chiefly in middle and later life and the low percentages in conditions found in the early decades of life. This same relationship can be seen to a lesser degree in other parts of this table.

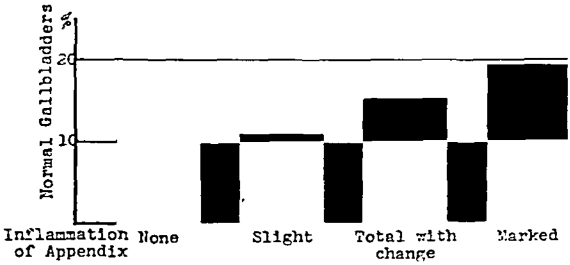

Chart 2.—Relation of inflammatory change in the appendix to the incidence of normal gallbladders. The incidence of the latter does not decrease in the presence of inflammatory change in the appendix.

INCIDENCE OF INFLAMMATORY CHANGE IN THE APPENDIX ACCORDING TO AGE

In discussing the relationship of inflammatory change in the appendix to age, the age groups from 1 to 10 and from 71 to 80 will be ignored because of the small number of patients in each. The total number in groups from 11 to 20 and from 61 to 70 were much smaller than in those remaining, but, since there are sufficient to figure percentages and in each the resultant figures fell well within the expected percentages, they have been used without weighting.

The incidence of the total number of appendixes showing inflammatory changes increased definitely with age. However, the incidence of those showing the various types of inflammation varied considerably from that in the total group. These differences are shown graphically in charts 3 to 16.

The increase of incidence of the appendixes with inflammatory change which occurred with an increase in age and the corresponding decrease in the number of appendixes without inflammatory change can be seen in chart 3 (solid lines). A more uniform decrease with age through the middle decades was found by eliminating the atrophic appendixes and considering only the normal appendixes. When the atrophic appendixes were added to those showing inflammatory change, a correspondingly more uniform increase of the changes in the appendix with age was obtained (broken lines). This is a better representation of the effect of age on the appendix.

Table 8.—*Effect of Inflammation Elsewhere in the Abdomen on the Incidence of Inflammation in the Appendix* *

			Condition in Appendix			
			No Inflammation		Inflammatory Change	
Condition Elsewhere in Abdomen		Total Cases	Number	Percentage	Number	Percentage
No inflammation		1,139	465	40.8	674	59.2
Inflammation		751	237	31.6	514	68.4
Salpingitis	451		147	32.1	306	67.9
Chronic salpingitis	327		125	38.2	202	61.8
Chronic supurative salpingitis	59		9	15.2	50	84.8
Acute salpingitis	65		11	18.5	54	81.5
Cholecystitis	235		74	31.5	161	68.5
Peptic ulcer	42		13	30.9	29	69.1
Tuberculous peritonitis or salpingitis	8		3	37.5	5	62.5
Peritonitis	7		1	14.3	6	85.7
Other types of inflammation	8		1	12.5	7	87.5
Totals		1,890	702	37.1	1,188	62.9

* For comparisons, read the vertical percentage columns. Apparently the incidence of inflammation in the appendix is increased slightly by the presence of inflammation elsewhere in the abdomen. This table is elaborated in tables 9 and 10.

The incidence of the total number of appendixes without inflammation decreased gradually with age (chart 4). The decrease in the incidence of normal appendixes was slightly more marked (chart 5). The increase in the incidence of atrophic appendixes with an increase in age is represented in chart 6.

The incidence of the total number of appendixes showing inflammatory change increased with age (chart 7). However, there was a fairly stationary period during middle life. The trend or complete lack of trend is much more definitely seen in the various groups which make up this total.

TABLE 9.—*Distribution of the Various Types of Inflammation Found in the Appendix According to the Type of Inflammation Found Elsewhere in the Abdomen*

	Condition in Appendix												
									Chronic Obliterative Appendicitis				
Condition Elsewhere in Abdomen	No Inflammation	Normal	Atrophic	Inflammation	Simple Chronic Appendicitis	Marked Inflammatory Changes	Chronic Catarrhal Appendicitis	Chronic Exudative Appendicitis	Acute Appendicitis	With Infiltration	Without Infiltration	Chronic Periappendicitis	Acute Periappendicitis	Total Cases
No inflammation..........................	465	415	50	674	320	354	55	94	23	59	119	4	0	1,139
Inflammation..............................	237	211	23	514	253	261	27	63	10	47	64	27	23	751
Salpingitis..............................	145	135	10	306	148	158	20	39	2	10	30	27	21	451
Chronic salpingitis..................	125	115	10	202	105	97	16	27	2	13	25	13	1	327
Chronic suppurative salpingitis.....	9	9	0	50	30	20	1	2	0	2	2	13	0	59
Acute salpingitis....................	11	11	0	54	13	41	3	10	0	4	3	1	20	65
Cholecystitis............................	74	63	11	161	80	81	7	18	7	19	30	0	0	235
Peptic ulcer.............................	13	12	1	29	13	16	0	5	0	7	4	0	0	42
Tuberculous peritonitis or salpingitis..	3	2	1	5	5	0	0	0	0	0	0	0	0	8
Peritonitis..............................	1	1	0	6	3	3	0	0	1	0	0	0	2	7
Other types of inflammation..........	1	1	0	7	4	3	0	1	0	2	0	0	0	8
Total appendixes..................	702	626	73	1,188	573	615	82	157	33	106	183	31	23	1,890

TABLE 10.—*Distribution of the Various Types of Inflammation Found in the Appendix According to the Type of Inflammation Found Elsewhere in the Abdomen (Percentages)* *

Condition Elsewhere in Abdomen	Total Cases	Condition in Appendix												
		No Inflammation	Normal	Atrophic	Inflammation	Simple Chronic Appendicitis	Marked Inflammatory Changes	Chronic Catarrhal Appendicitis	Chronic Exudative Appendicitis	Acute Appendicitis	Chronic Obliterative Appendicitis		Chronic Periappendicitis	Acute Periappendicitis
											With Infiltration	Without Infiltration		
No inflammation	1,139	40.82	36.52	4.30	59.18	28.10	31.10	4.83	8.25	2.02	5.18	10.45	0.35	0.00
Inflammation	751	31.56	28.50	3.06	68.44	33.69	34.75	3.59	8.30	1.33	6.26	8.52	3.59	3.06
Salpingitis	451	32.15	29.94	2.21	67.85	32.82	35.03	4.21	8.63	0.44	4.21	6.65	5.99	4.65
Chronic salpingitis	327	38.22	35.32	2.90	61.78	32.12	29.66	4.90	8.30	0.62	3.98	7.65	3.98	0.32
Chronic suppurative salpingitis	59	15.25	15.25	0.00	84.75	50.85	33.90	1.69	3.39	0.00	3.39	3.39	22.03	0.00
Acute salpingitis	65	18.46	18.46	0.00	81.54	18.46	63.08	4.62	14.62	0.00	6.15	4.62	1.51	29.24
Cholecystitis	235	31.49	26.81	4.68	68.51	34.04	34.47	2.98	7.67	2.98	8.09	12.77	0.00	0.00
Peptic ulcer	42	30.95	28.27	2.38	69.05	30.96	38.09	0.00	11.90	0.00	16.67	9.52	0.00	0.00
Tuberculous peritonitis or salpingitis	8	37.50	25.00	12.50	62.50	62.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Peritonitis	7	14.29	14.29	0.00	85.71	42.85	42.85	0.00	0.00	14.29	0.00	0.00	0.00	28.58
Other types of inflammation	8	12.50	12.50	0.00	87.50	50.00	37.50	0.00	12.50	0.00	25.00	0.00	0.00	0.00
Figures for whole group	1,890	37.15	33.28	3.87	62.85	30.31	32.54	4.34	8.31	1.75	5.61	9.68	1.61	1.22

* The percentage incidence was calculated on the total number of appendixes classified with each type of inflammation elsewhere in the abdomen. For comparisons, read the vertical columns.

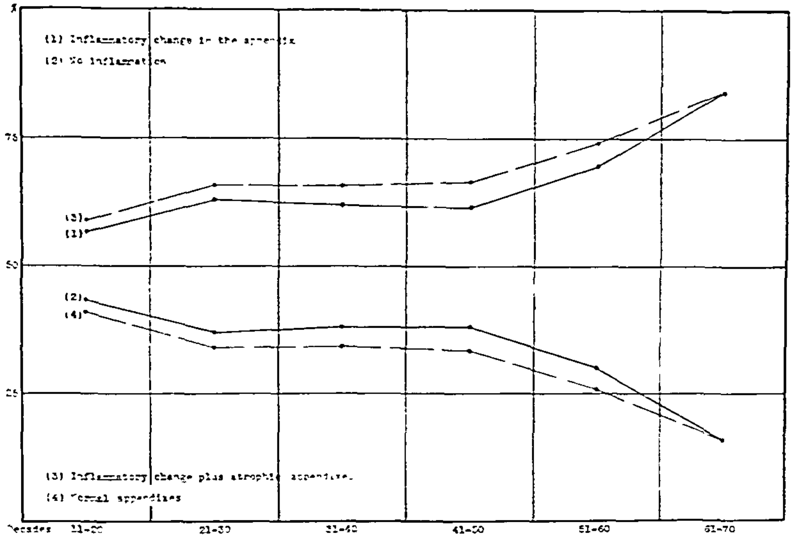

Chart 3.—The effect of age on the incidence of changes in the appendix. The comparison is shown of *no inflammation to inflammatory change* (*solid lines*) and also of normal appendixes to those showing atrophic and inflammatory change (broken lines).

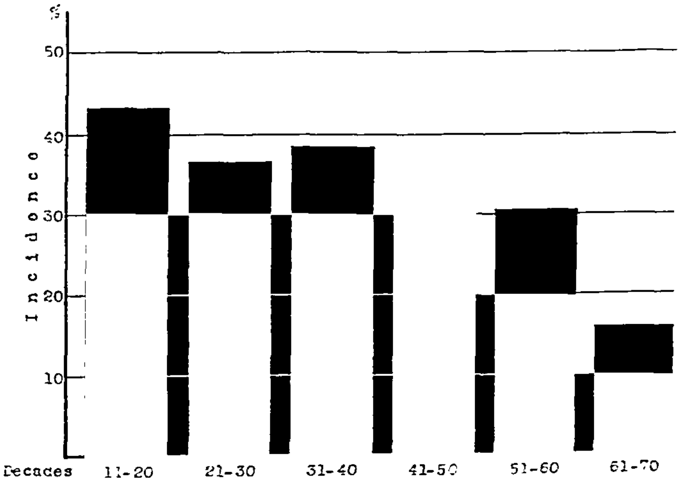

Chart 4.—Incidence of appendixes which presented no inflammatory change according to age.

There was a slight but definite decrease in the incidence of simple chronic appendicitis with age (chart 8). This might be accounted for by the fact that appendixes with more marked pathologic processes as age increases come from this group as well as from the group of normal appendixes. The total number of appendixes with marked changes increased in incidence with age (chart 9). There was a slight increase in the incidence of chronic catarrhal appendicitis with an increase in age (chart 10). There was a marked increase with age in the incidence of chronic obliterative appendicitis, both with (chart 11) and without infiltration (chart 12). The incidence of chronic exudative appendicitis (chart 13) and acute appendicitis (chart 14) showed a spread

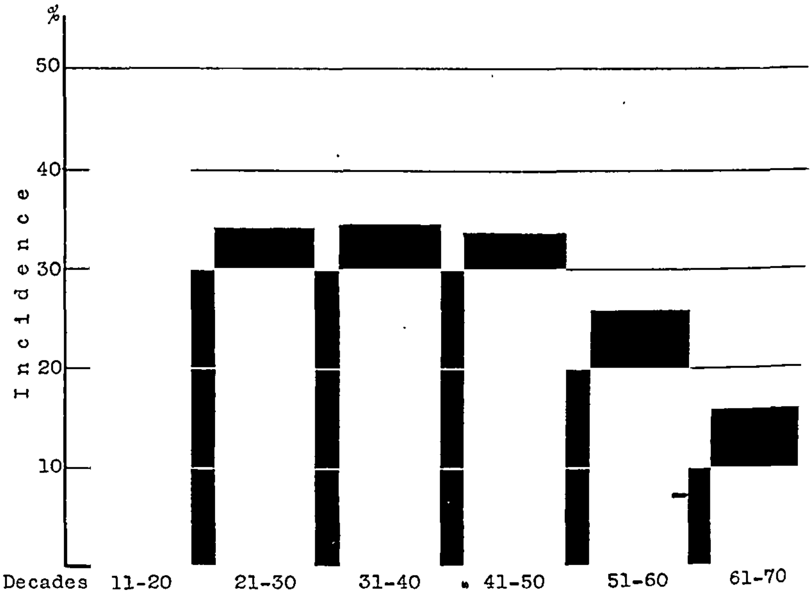

Chart 5.—Incidence of normal appendixes according to age. Those appendixes which were relatively normal, i. e., showed no definite inflammatory change, were also included.

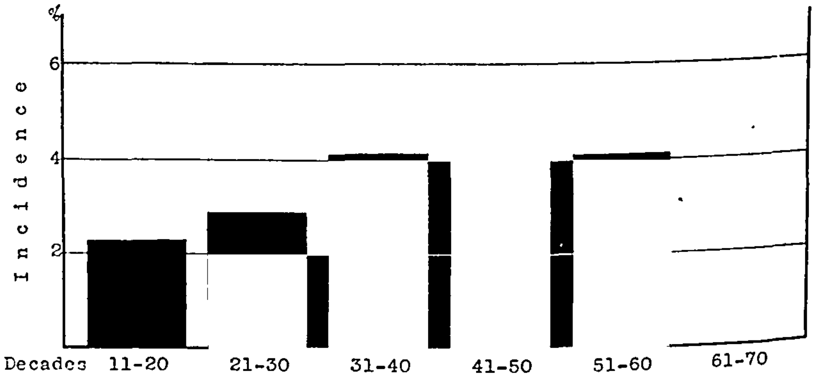

Chart 6.—Incidence of atrophic appendixes according to age.

throughout, indicating that age had no effect. This is of particular interest as pathologically these conditions are closely related.

There was an increase in the incidence of periappendicitis, both chronic (chart 15) and acute (chart 16), in the early age group and a marked decrease with age. This is exactly as would be expected, because, as mentioned earlier, the causes of periappendicitis are largely conditions occurring in early and early middle life.

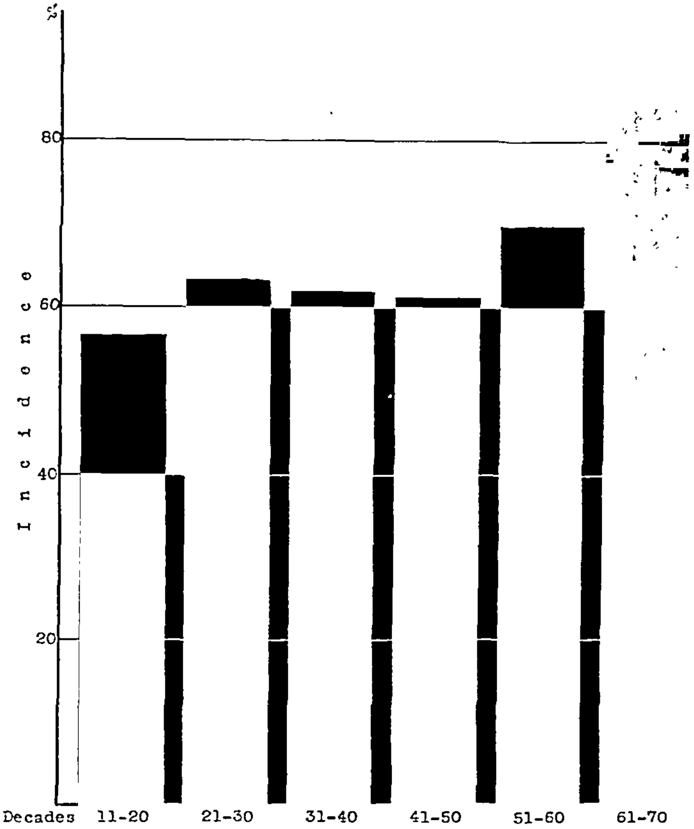

Chart 7.—Incidence of total appendixes with inflammatory change according to age.

To summarize the effect of age on the incidence of inflammatory changes found in these appendixes:

There was an increased incidence of inflammatory change with increasing age of the patients from whom the appendixes were removed (charts 3 and 7). This increase in pathologic change was found slightly greater when the appendixes which showed atrophic changes were added to those showing inflammatory change (chart 3).

The incidence of appendixes without inflammatory change (charts 3 and 4) and of the appendixes with chronic periappendicitis (chart 15) and acute periappendicitis (chart 16) decreased with increasing age.

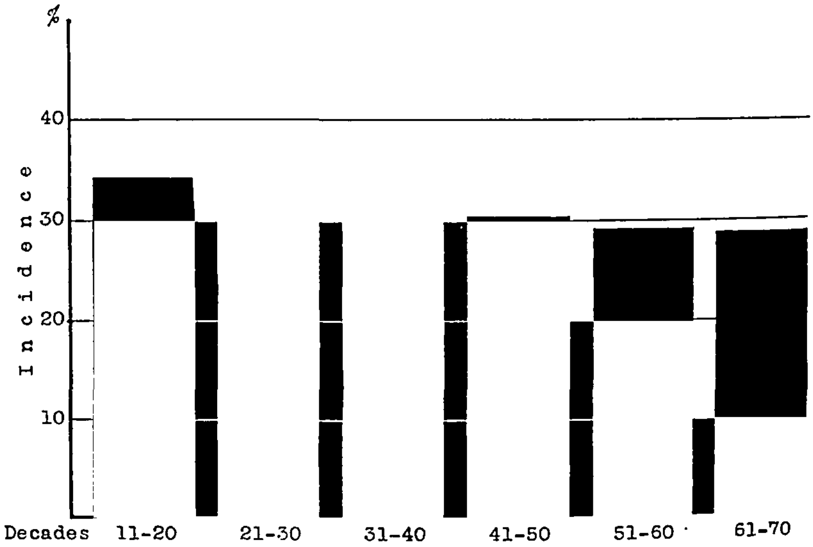

Chart 8.—Incidence of simple chronic appendicitis according to age.

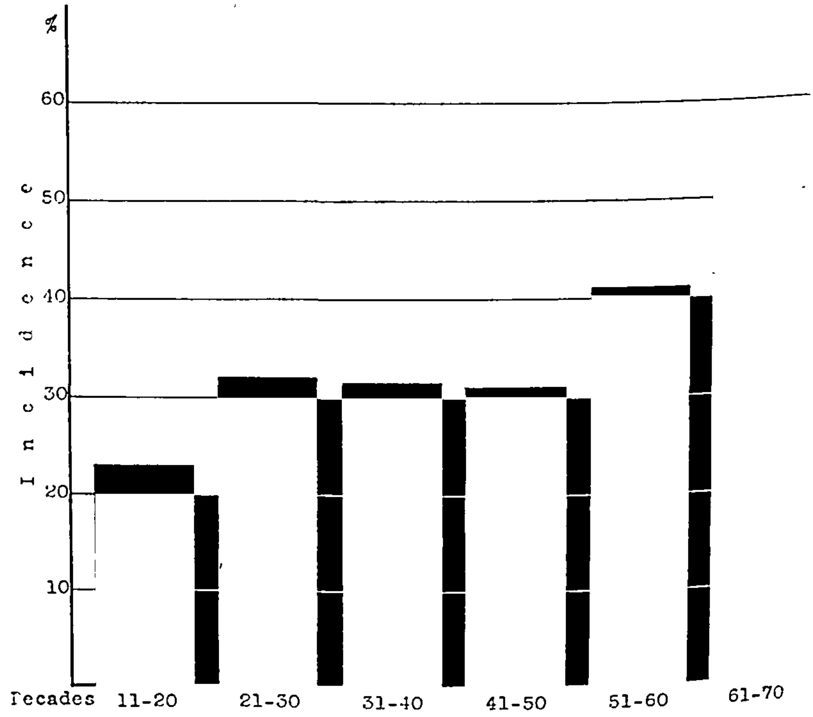

Chart 9.—Incidence of appendixes with marked inflammatory change according to age.

The incidence of chronic exudative appendicitis (chart 9) and acute appendicitis (chart 10) showed no increase with an increase in age.

TABLE 11.—*Incidence of Inflammatory Change in the Appendix According to Age*

Age by Decades	Condition in Appendix													
	No Inflammation	Normal	Atrophic	Inflammation	Simple Chronic Appendicitis	Marked Inflammatory Changes	Chronic Catarrhal Appendicitis	Chronic Exudative Appendicitis	Acute Appendicitis	Chronic Obliterative Appendicitis		Chronic Periappendicitis	Acute Periappendicitis	Total Cases
										With Infiltration	Without Infiltration			
1 to 10	1	1	0	4	2	2	0	0	1	0	0	0	1	5
11 to 20	19	18	1	25	15	10	0	3	1	0	1	1	4	41
21 to 30	151	139	12	258	127	131	20	38	3	14	27	16	13	409
31 to 40	271	215	20	441	215	226	41	56	17	34	63	12	3	715
41 to 50	207	182	25	331	163	168	10	40	8	39	68	2	1	538
51 to 60	46	40	6	106	43	63	9	18	3	13	19	0	1	152
61 to 70	4	4	0	21	7	14	2	2	0	6	4	0	0	25
71 to 80	0	0	0	2	1	1	0	0	0	0	1	0	0	2
Totals	702	629	73	1,188	573	615	82	157	33	106	183	31	23	1,890

TABLE 12.—*Percentage Incidence of Various Types of Inflammatory Change in the Appendix According to Age* *

Age by Decades	Total Cases	Condition in Appendix											
		No Inflammation	Normal	Atrophic	Inflammation	Simple Chronic Appendicitis	Marked Inflammatory Changes	Chronic Catarrhal Appendicitis	Chronic Exudative Appendicitis	Acute Appendicitis	Chronic Obliterative Appendicitis		Chronic Periappendicitis	Acute Periappendicitis
											With Infiltration	Without Infiltration		
1 to 10	5	20.00	20.00	0.00	80 00	40.00	40.00	0.00	0.00	20.00	0.00	0.00	0.00	20.00
11 to 20	41	43.18	40.91	2.27	56.82	34.09	22.73	0.00	6.82	2.28	0.00	2.28	2.28	9.07
21 to 30	409	36.82	33.98	2.81	63.18	31.05	32.13	4.89	9.29	0.74	3.42	6.64	3.91	3.18
31 to 40	715	38.32	34.23	4.09	61.68	30.07	31.01	5.73	7.83	2.38	4.76	8.81	1.68	0.42
41 to 50	538	38.47	33.83	4.64	61.53	30.29	31.24	1.85	7.44	1.49	7.25	12.64	0.37	0.18
51 to 60	152	30.26	26.18	4.08	69.74	28.29	41.45	5.92	11.84	1.97	8.56	12.50	0.00	0.66
61 to 70	25	16.00	16.00	0.00	84.00	28.00	56.00	8.00	8.00	0.00	24.00	16.00	0.00	0.00
71 to 80	2	0.00	0.00	0.00	100.00	50.00	0.00	0.00	0.00	0.00	0.00	50.00	0.00	0.00
Totals	1,890	37.15	33.28	3.87	62.85	30.31	32.54	4.34	8.31	1.75	5.61	9.68	1.64	1.22

* The percentages were calculated on the total number of appendixes in each decade. This table is shown graphically in charts 3 to 16.

The incidence of appendixes with inflammatory change (chart 7) and those with marked inflammatory change (chart 9) increased with age; there was also a similar increase in the incidence of chronic catarrhal appendicitis (chart 10), atrophic appendicitis (chart 6), chronic obliterative appendicitis without infiltration (chart 12) and chronic obliterative appendicitis with infiltration (chart 11).

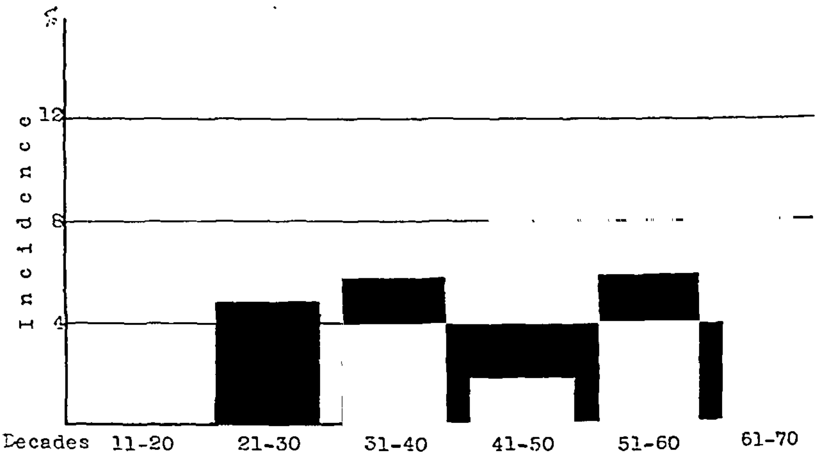

Chart 10.—Incidence of chronic catarrhal appendicitis according to age.

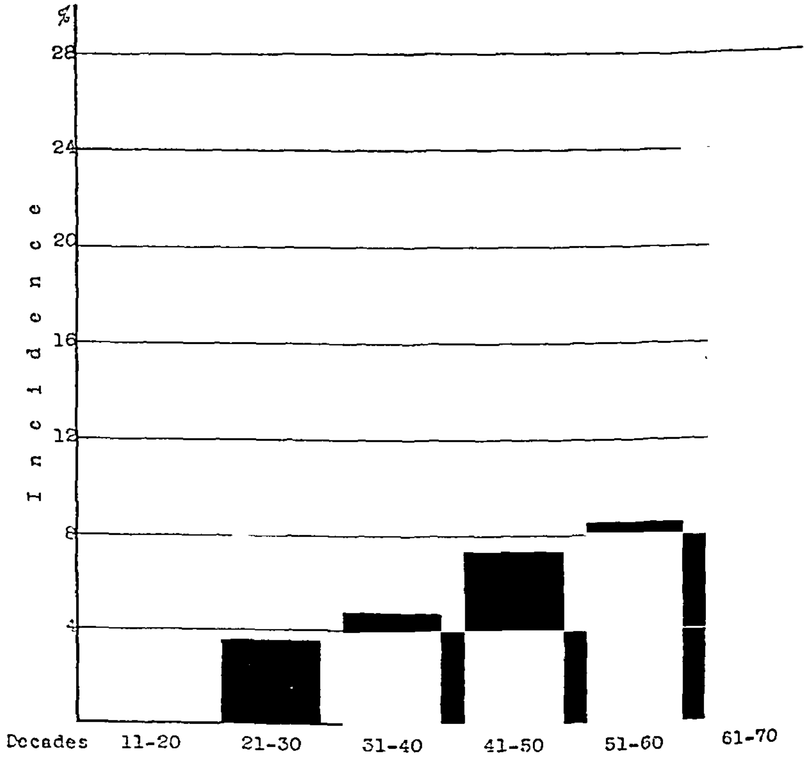

Chart 11.—Incidence of chronic obliterative appendicitis with infiltration according to age.

OTHER PATHOLOGIC CONDITIONS

Oxyuris in the Lumen of the Appendix.—Three appendixes were found to contain Oxyuris in the lumen, an incidence of 0.2 per cent. The pathologic conditions in these appendixes were classified as follows: simple chronic appendicitis, chronic obliterative appendicitis with infiltration and acute catarrhal appendicitis. Two of the patients were operated on because of retroversion of the uterus and the other because of an ovarian cyst. Their ages were 30, 30 and 32 years.

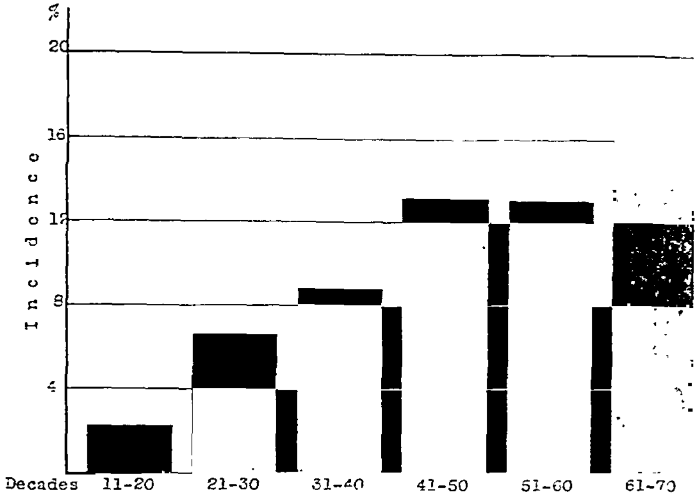

Chart 12.—Incidence of chronic obliterative appendicitis without infiltration according to age.

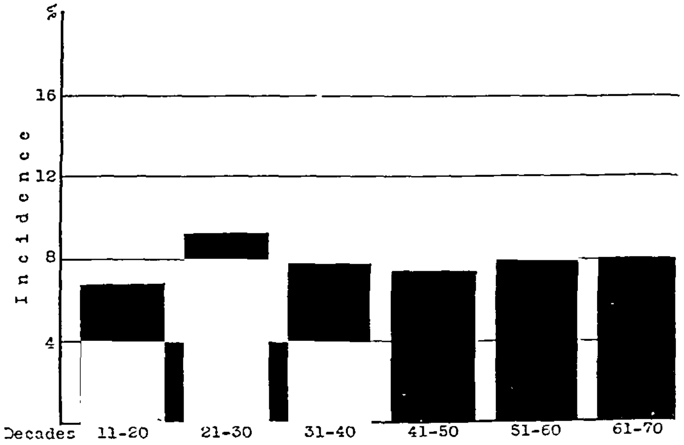

Chart 13.—Incidence of chronic exudative appendicitis according to age.

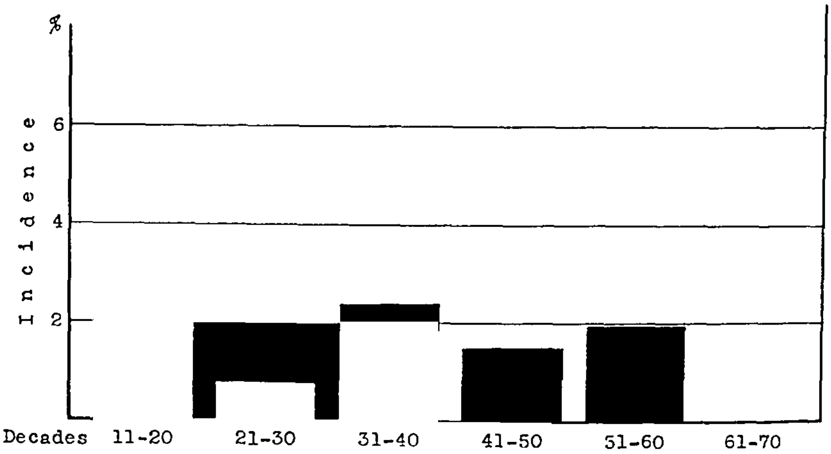

Chart 14.—Incidence of acute appendicitis according to age.

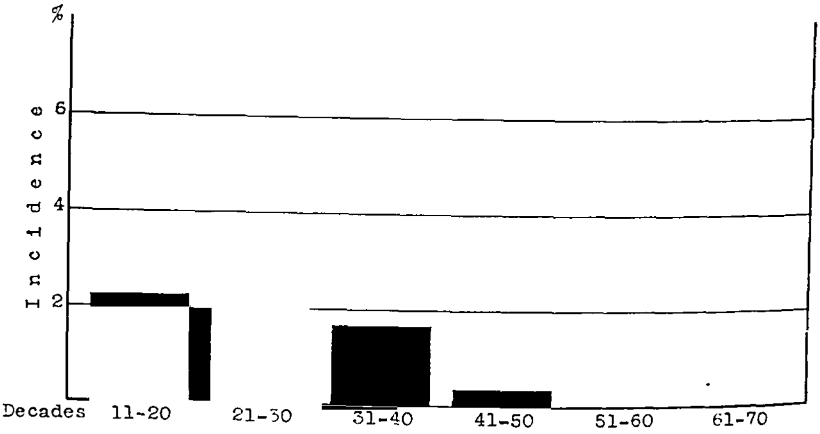

Chart 15.—Incidence of chronic periappendicitis according to age.

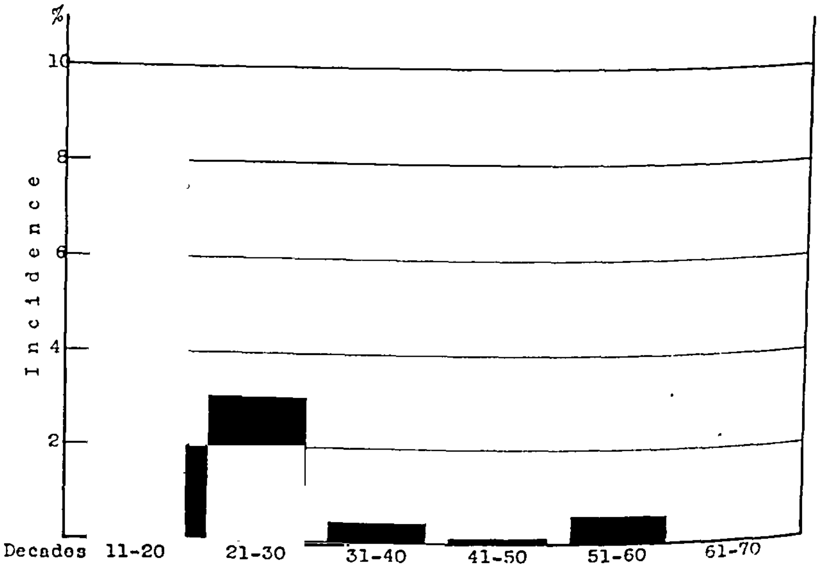

Chart 16.—Incidence of acute periappendicitis according to age.

Mucocele of the Appendix.—Mucoceles were found in 3 appendixes, an incidence of 0.2 per cent. One patient was operated on for intestinal obstruction due to adhesions and the other 2 for fibromyomata uteri. Their ages were 30, 44 and 75 years.

Tuberculosis of the Appendix.—This condition was found in 5 appendixes, an incidence of 0.3 per cent. Three appendixes showed chronic tuberculous appendicitis when no other tuberculous condition was noted in the abdomen. One was removed at the same time as the gallbladder, a diagnosis of chronic cholecystitis with cholelithiasis having been made. Another was removed at an operation for chronic salpingitis, but microscopic examination revealed no evidence of tuberculosis. The third was removed at the time of an operation for fibromyomata uteri.

TABLE 13.—*Pathologic Conditions Found in the Appendix, Other Than Inflammatory Change or Its Absence, With Incidence* *

Pathologic Condition	Number of Cases	Incidence, Percentage	Number of Deaths	Mortality, Percentage
Oxyuris in the lumen	3	0.16	0	0.00
Mucocele	3	0.16	0	0.00
Tuberculosis	5	0.26	1	20.00
Diverticulum	1	0.05	0	0.00
Hyperplasia of the mucosa	3	0.16	0	0.00
Tumors	6	0.32	0	0.00
Totals	21	1.11	1	4.76

* *The incidence was calculated on the basis of the 1,904 appendixes examined microscopically.*

I repeat for emphasis that the histories and physical examinations in these 3 cases and in the following cases revealed no symptom or sign referable to the appendix.

The fourth appendix presented chronic tuberculous appendicitis in conjunction with a tuberculous cecum, the original operation having been done for fibromyomata uteri and retroversion.

The fifth appendix was removed from a patient who had acute tuberculous peritonitis. Microscopically it showed subacute tuberculous appendicitis. The patient died of generalized tuberculosis.

The age incidence in these cases was 20, 32, 35, 38 and 42 years.

Syphilis.—Microscopic evidence of syphilis was not found throughout the series, although a number of the patients had positive Wassermann reactions.

Diverticulum of the Appendix.—One appendix contained a diverticulum, an incidence of 0.1 per cent. The original cause for operation was ectopic endometrium on the pelvic peritoneum. The patient was 34 years old.

Hyperplasia of the Mucosa.—Three appendixes showed marked hyperplasia of the mucosa, an incidence of 0.2 per cent; in 1 instance it was described as papillary and in the other as adenomatous. This condition follows an inflammatory process and cannot be classified as a new growth in this stage. Two of the primary operations were performed for fibromyomata uteri and 1 for a parovarian cyst. The ages of these patients were 26, 38 and 42 years.

Tumors of the Appendix (table 14).—Four appendixes showed endometrial rests, an incidence of 0.2 per cent. Three were from patients operated on for fibromyomata uteri and the other from a patient operated on for retroversion and chronic salpingitis. Their ages were 38, 42, 44 and 50 years.

A carcinoid of the appendix (an incidence of 0.1 per cent) was found in a patient 45 years old who was operated on for fibromyomata uteri.

One appendix contained a papillary adenoma, possibly malignant (an incidence of 0.1 per cent). The patient, aged 26, was operated on because of a tubal pregnancy.

TABLE 14.—*Types of Tumors Found in the Appendixes Studied, With Their Incidence* *

Tumor	Number of Cases	Incidence, Percentage	Number of Deaths
Endometrial rests	4	0.21	0
Carcinoid	1	0.05	0
Papillary adenoma, possibly malignant	1	0.05	0

* This was calculated on the basis of the 1,904 examined microscopically.

It is of interest that none of the 1,904 appendixes examined microscopically showed a definite malignant process and that only 2 contained lesions which were questionably malignant.

SUMMARY AND CONCLUSIONS

Statistics on a group of 2,065 incidental appendectomies have been presented. These appendectomies were performed on patients whose histories and physical examinations gave no evidence of past or present appendical disease. The appendectomies included all those falling within the described definition which were done at St. Luke's Hospital (from both the private pavillion and the wards) in eleven years (1925 to 1935 inclusive). The pathologic conditions found in the 1,904 appendixes examined microscopically have been presented in the various tables and charts.

These findings may be stated briefly as follows: One third of the appendixes were either normal or relatively normal. Just less than one third showed slight to moderate, but definite, inflammation (simple chronic appendicitis). Over one third presented evidence of marked pathologic change. The latter group included those with types of appendicitis other than simple chronic appendicitis, together with atrophic appendixes and those which showed other pathologic conditions, as listed in table 13.

Inflammatory changes are found in a considerable percentage of appendixes in the absence of a history or physical findings indicative of a pathologic condition in the right lower abdominal quadrant. In this series, 62 per cent fell within this class. More than half (51 per cent) of these showed marked inflammatory changes (32 per cent of the total number).

A slight but definite increase in inflammatory change in the appendix occurs in the presence of inflammation elsewhere in the abdomen. This becomes a marked increase with chronic suppurative and acute salpingitis and with peritonitis.

Acute appendicitis, even with actual suppuration, can exist without any subjective or objective evidence of its presence. The incidence was 1.7 per cent in this series.

A study of the cases in which the gallbladder was removed showed no increase in the incidence of cholecystitis in the presence of inflammation in the appendix. From this finding the statement can be made positively that no evidence is found to indicate that inflammation in the appendix causes inflammation in the gallbladder.

With increasing age there is a definite increase in the incidence of atrophic and inflammatory changes in the appendix. This is most marked with chronic obliterative appendicitis. It does not hold true for periappendicitis, which is caused by conditions prone to occur in early and early middle life.

The incidence of pathologic change other than inflammation is very low. This would indicate that these other conditions ordinarily produce symptoms referable to disease in the appendix.

When the appendix is not the cause of symptoms and there is no inflammation elsewhere in the abdomen, the expected incidence of pathologic change in the appendix is represented by the top row of figures in table 10. I shall refer to these figures in a study of the symptom complex attributed to chronic appendicitis.

Although the figures are not presented, I feel that it is worth while to mention the fact that the incidence of postoperative complications was found to be no greater than would be expected in a similar list of operations in which appendectomy was not performed. Also, no increase in mortality was found. From this the conclusion may be drawn that in properly selected cases, i. e.. in those in which the nature of the operation and the patient's condition are favorable. the incidental removal of the appendix is a safe and worth while procedure.

The pathologic examination of all the appendixes listed in this paper was made by Dr. Leila C. Knox, pathologist at St. Luke's Hospital.

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CHRONIC FUNCTIONAL LESIONS OF THE SHOULDER

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It is difficult to find a title sufficiently noncommittal and inclusive and yet specific enough to designate the things I wish to consider. The word chronic in the title is used in a literal sense and entirely without any implication of disease, although some of the bony changes associated with these lesions simulate some of those commonly attributed to arthritis. I believe that the lesions here considered are not primarily or to any considerable degree due to the extraordinary uses to which the upper extremities are put but are caused merely by the ordinary, often repeated, everyday uses. They are hour to hour, day to day, month to month, year to year and decade to decade effects. It must not be overlooked, however, that some of the structures affected by function may be weakened gradually and eventually rupture under relatively slight strains, evoking symptoms out of all proportion to the forces involved at the time.

In considering the production of the lesions in question, one must divest oneself of the idea that the shoulder joint is a marvel of mechanical perfection. Even a cursory survey of its architecture should correct such a mistaken view. One may, I presume, grant that the human shoulder may be adapted perfectly to the uses for which it may have been intended, but certainly no one can rightly maintain that it is perfectly adapted for the uses to which it is put. These uses require a truly universal joint, and the humeroscapular articulation is such a one only imperfectly and only by subjecting the surrounding soft parts to repeated trauma. Even slight trauma recurring in the same place for hours, days, weeks and months has a cumulative effect and may produce great changes. It is hence no wonder that the reparative powers of the structures concerned often are exceeded and that repeated slight trauma may provoke an obliterative endarteritis and sclerosis. Moreover, since the individual trauma may fall below the threshold of reflex protective responses, there may be little to forestall the cumulative effect, and it is important to remember that it is the repetition and not the range of motion that counts.

Although I shall confine my remarks to the shoulder, I do not mean to imply that the functional lesions under consideration here occur nowhere else in the body. They are commonest and most pronounced

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in the shoulder and also seem to occasion the greatest amount of discomfort and disability there. Some of them may occur anywhere else where motion is possible, no matter how slight the range, and they always become evident to the unaided eye after adequate repetition of the motion. However, I have seldom noticed them before the third decade of life. The average age of the bodies from which the specimens for the illustrations were taken was over 60 years.

LESIONS CONCERNED

The lesions vary greatly in their intensity and manifestations from joint to joint and person to person. Although abnormal or pathologic conditions may facilitate and also markedly accentuate them, I am deliberately excluding changes due to disease and am confining my attention to the effects of normal use alone. In the last analysis, of course, these lesions are traumatic, but they are not that in the customary meaning of that word. They undoubtedly are not accompanied by hemorrhage or some other phenomena associated with lesions ordinarily regarded as traumatic; yet the distinction is quantitative rather than qualitative. Among the lesions concerned are the following:

1. Fraying and partial destruction of the inner surface of the walls of the subdeltoid bursa and of the supra-acromial bursa, when present, and of the deeper bursae about the shoulder.
2. Fraying and partial or complete destruction of considerable portions of the articular capsule, both from within and from without, and of the coracohumeral and the inconstant superior and middle glenohumeral ligaments.
3. Fraying and partial or complete division or detachment of the tendon of the supraspinatus and partial destruction of that of the infraspinatus and of the long tendon of the biceps and that of the subscapularis.
4. Partial or complete erosion of the coraco-acromial ligament.
5. Perforation of the acromioclavicular articulation below and complete destruction of the deeper portion of the articular capsule.
6. Partial or complete dislocation of the pretubercular and the intertubercular portions of the long tendon of the biceps.
7. Thinning and complete local destruction of the articular cartilages, both hyaline and fibroid, in the humeroscapular and the acromioclavicular articulations.
8. Fraying of the under surface of the deltoid muscle and complete destruction of a large part of its middle portion.
9. Polishing and eburnation of the bony surfaces that come into movable contact after destruction of the overlying or intervening soft parts and cartilages.
10. Partial or total destruction of the articular fibrocartilage and of the articular disk and the cartilage on the clavicle and acromion; opening of the acromioclavicular joint from below with or without bony polishing, sometimes even in cases of ununited acromions.
11. Formation of a true coracoclavicular articulation with or without bony contact between the clavicle and the coracoid process and consequent polishing.
12. Polishing of the coracoid process from contact with the head and tuberosities of the humerus.
13. Considerable loss of bone from wear in the areas of bony contact.

CONDITION OF BURSAE

An anatomist seldom encounters smooth superficial synovial bursae in cadavers past middle age. Since the amount of fluid in a normal bursa is limited to mere moistening of its internal surface, normal bursae are not distended, and their walls hence are constantly in contact with each other except for a thin film of fluid. Were they lined by a layer of epithelium, endothelium or highly specialized mesothelium, such as that in the peritoneum, pleura and pericardium resting on a subserosa, one might expect the bounding membranes to become detached from the connective tissue on which they rest, but the absence of such a mesothelium and basement membrane and the existence of a gradual transition from the surface layer of flattened, stellate mesothelium to ordinary connective tissue make such a separation impossible. It follows from this that he who does a "synovectomy" really does not remove a membrane but merely destroys the innermost portion of the connective tissue of an articular capsule.

Instead of a smooth inner surface in synovial bursae, roughening and fraying and complete destruction of it are frequently encountered. Such conditions commonly exist in the subacromial and the supracapsular portion of the subdeltoid bursa and may be present in any or most of the thirteen or more bursae which may be associated with the humeroscapular articulation. It is mainly these portions of the surfaces of the subdeltoid bursa which are brought into firm contact with every abduction of the arm. Hence the rest of the roof and the floor of the bursa usually are intact and normal, even after the entire upper portion of the articular capsule has been destroyed and when bony polishing is present on the tuberosital portion of the humerus which comes into contact with the acromion. Whenever the subdeltoid bursa is large, it extends distally onto the shaft of the humerus beyond the tuberosities and under the coracoid process, but the walls of this portion may then also be wholly preserved. The areas of most intimate and frequent contact are always the first to show change, although it sometimes happens that one of three possible independent subcoracoid bursae may show complete destruction of its smooth inner surface, although the smooth surface of the two other contiguous bursae may be unaffected. It has often been asserted that roughening and destruction of the normal walls of bursae are the result of inflammation, or bursitis. While recognizing fully the changes that may be effected by chronic inflammation in bursae, the lesions here considered manifestly were not produced in that way, and it is well to emphasize that long-continued movement of soft parts on each other frequently effects roughening and fraying of the apposed structures. This, to be sure, applies also to articular cartilages, both hyaline and fibroid.

It is of great significance that similar effects of wear are met with also between structures which normally are not separated by bursae, such as the radius and the muscles and the tendons of the long abductor and the long and short extensor muscles of the thumb and the extensor carpi radialis longus muscle. Such an instance is represented in figure 1, a photograph of a specimen taken from a right forearm which showed no evidence of any pathologic condition or of injury, past or present. It will be recalled that loose connective tissue normally separates these structures in this region of the antibrachium. This tissue evidently was destroyed and the coapted surfaces of the muscles and tendons frayed by wear from often repeated rotation of the radius. This may have occurred under the pressure of a sling, a lever or a snugly fitting arm band, although probably none of these things are indispensable factors.

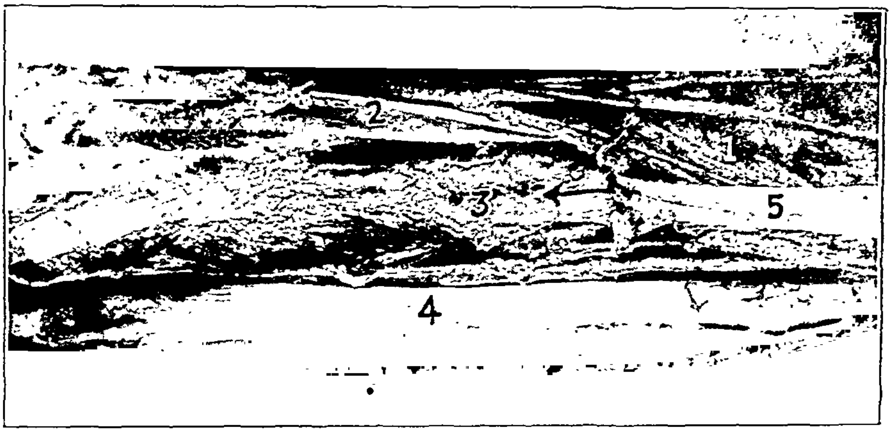

Fig. 1.—Fraying on the surfaces of the tendons and bellies of the abductor pollicis longus, the flexor pollicis longus, the extensor pollicis brevis and the extensor carpi radialis longus and of the loose connective tissue and the underlying periosteum in the left arm of a man 44 years of age. The tendon of the brachioradialis was reflected distally, and the photograph was taken from the side and in front with the forearm in semipronation. The belly of the abductor pollicis longus is indicated by *1*, the deeper surface of the extensor carpi radialis longus and brevis by *2*, the belly of the flexor pollicis longus by *3*, the tendon of the flexor carpi radialis by *4*, the tendon of the brachioradialis, reflected, by *5* and the tendon of the palmaris longus, on the edge, by *6*. The arrow points to the most deeply worn portion of *3*.

CAPSULAR DEFECTS

The forces which destroy synovial surfaces must of necessity produce similar effects on the underlying or deeper, outer bounding structures. Hence the articular capsule of the shoulder and the associated tendons may become similarly affected. The superficial surface of the portion of the capsule immediately proximal to the greater tuberosity usually is the one to suffer roughening and fraying first, although roughening may also be evident on the inner surface of the capsule where it comes into contact with the margin of the articular cartilage. Thinning of the capsule and of the tendon of the supraspinatus muscle likewise usually occurs first proximal to the greater tuberosity, and perforation of the tendon and capsule usually is first seen here, as shown in figure 2. It may, however, also occur more ventrally or anteriorly to the tendon of the supraspinatus muscle in the region under the coracoid process and even in the dorsal portion of the capsule, which is associated with the tendon of the infraspinatus muscle, as shown in figures 3 and 4 and represented by Meyer[1] in

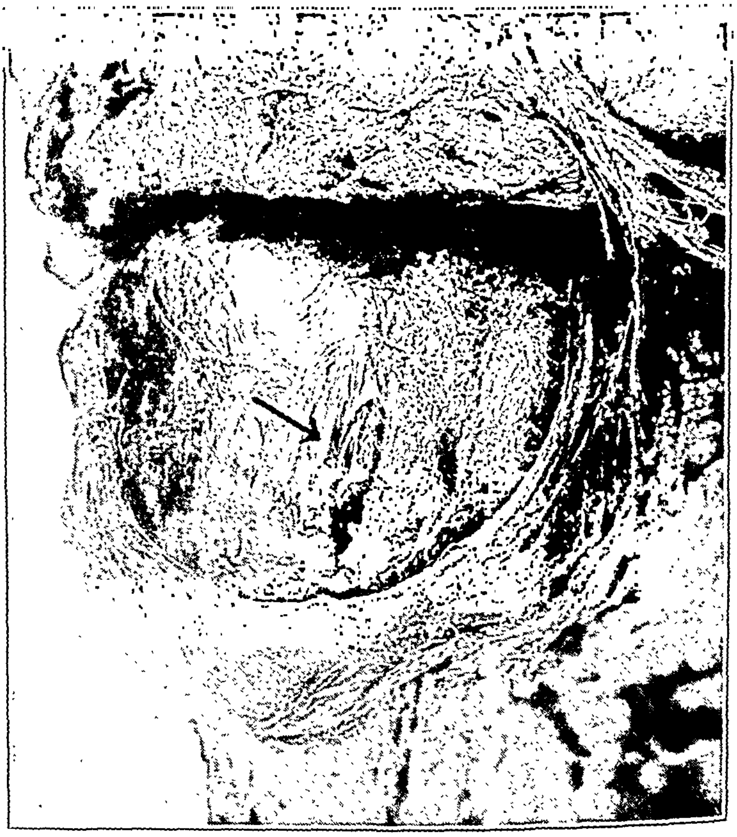

Fig. 2.—Fraying of the inner surface of the subdeltoid bursa and an oval defect in the distal portion of the supraspinatus tendon with its long diameter in a longitudinal direction, indicated by the arrow.

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[1] Meyer, A. W.: Further Observations upon Use-Destruction in Joints, J. Bone & Joint Surg. **4**:491-511, 1922. See also: Meyer, A. W.: Anatomical Specimens of Unusual Clinical Interest, Am. J. Orthop. Surg. **13**:86-95, 1915; Further Evidence of Attrition in the Human Body, Am. J. Anat. **34**:241-267, 1924; Spontaneous Dislocation of the Tendon of the Long Head of the Biceps Brachii: Report of Four Cases, Arch. Surg. **13**:109-119 (July) 1926; The Minuter Anatomy of Attrition Lesions, J. Bone & Joint Surg. **13**:341-360, 1931.

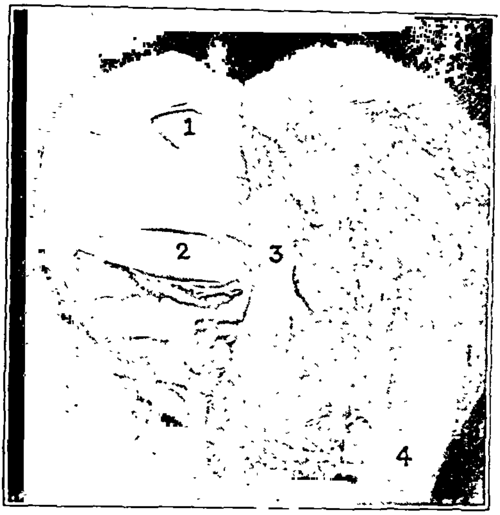

Fig. 3.—Right shoulder viewed from above, showing defects in the articular capsule anterior and posterior to the unruptured *tendon of the supraspinatus*. The dorsal defect is indicated by *1*, the long tendon of the biceps lying in a large ventral defect, by *2*, the coraco-acromial ligament by *3* and the clavicle by *4*.

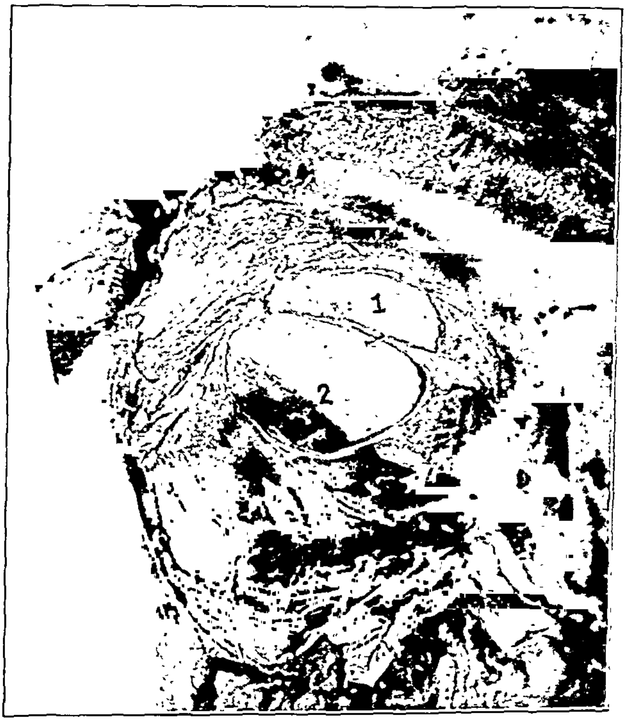

Fig. 4.—Two large attrition defects (*1* and *2*) in the dorsal portion of the capsule of the shoulder. The tendons of the infraspinatus and teres minor were practically intact. The cartilaginous margin of the head of the humerus responsible for these defects can be seen clearly across the lower defect, forming a slightly irregular border below *2*. The two defects are separated by a narrow strip of capsule on either side of which the (white) articular cartilage of the head of the humerus can be seen.

figures 8 and 9. The latter defects always are produced from within but the former largely from without, and they may be present when all the other articular structures are practically normal. Whenever the margin of the acromion or its under surface is rough or studded with small periosteal osteophytes, the superficial layer of the capsule, the tendon of the supraspinatus muscle and the deepèr, thicker portion of the capsule, which may all be detached from each other, forming separate layers, may show parallel longitudinal scoring or ribboning, as shown in figures 5 and 6.

In cases of maximal capsular destruction, the entire upper portion is absent, the tendon of the infraspinatus muscle is forced backward and downward and that of the subscapularis muscle may be detached completely from the lesser tuberosity, maintaining its attachment to the adjacent diaphysis only. However, one can always find the retracted, more proximal, portion of the capsule under the acromion, for although retracted and sometimes somewhat folded, it always presents a thin, sclerotic, falciform border.

It is of much moment in connection with the causation of capsular defects into the shoulder joint from above that they may occur on either side of an unruptured and intact tendon of the supraspinatus muscle. Sometimes they are present on both sides of this tendon and may be represented by mere longitudinal slits, such as those represented at *2* and *3* in figure *7* and in figure 8. The character and direction of these defects show that they could not have been produced by pull of the muscle or rupture of a tendon, least of all by rupture of that of the supraspinatus, and the entire absence of evidence of disease in these cases shows that it cannot have been a factor in their production.

Whenever the periosteum distal to the capsular and tendinous attachment on the greater tuberosity of the humerus and that under the acromion are destroyed through contact, polishing and eburnation of the underlying bone are inevitable if adequate motion continues. Since the periosteum possesses marked osteogenetic powers, small osteophytes or exostoses not infrequently develop in the areas undergoing denudation if the necessary conditions prevail. This is what one should expect, and whenever osseous roughening occurs on the distal margin or the under surface of the acromion, the destruction of the superficial layer of the joint capsule is greatly facilitated and so is that of the tendon of the supraspinatus and the deeper, thicker portion of the capsule and of the capitular articular cartilage when it comes into contact with the acromion. This does not imply, however, that the articular cartilage on the head of the humerus may not be worn away elsewhere, for this frequently is the case.

After destruction of the upper portion of the articular capsule and its included tendons, the deeper surface of the deltoid muscle will be

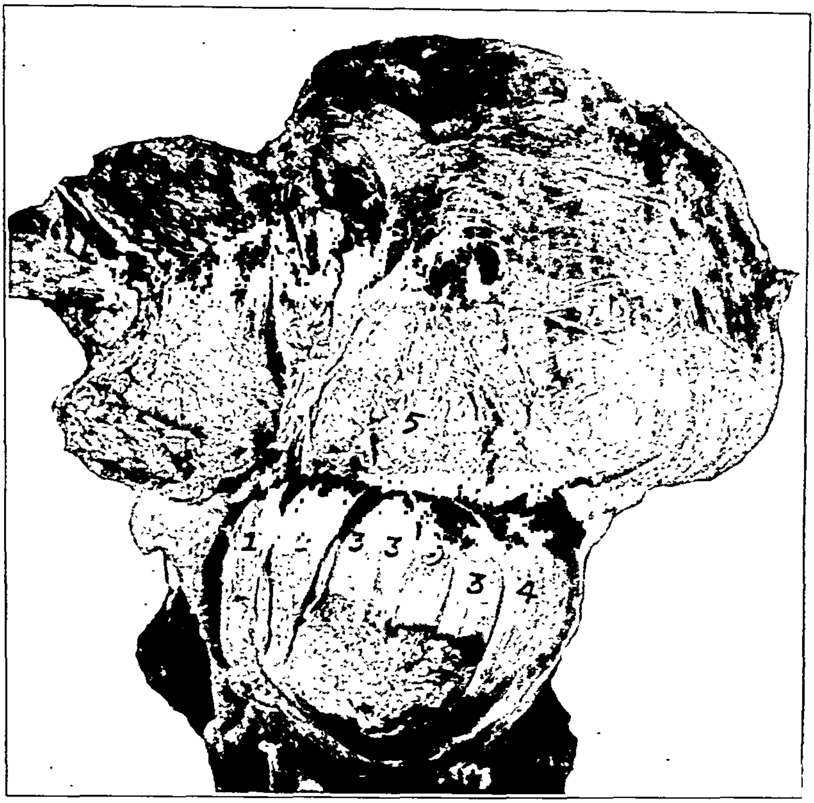

Fig. 5.—Right shoulder with the deltoid reflected upward, revealing a large oval defect in the tendon of the supraspinatus bordered by smooth, sharp-edged margins of the latter (*2*) and (*4*), below which lie longitudinal ribbons of the deeper portion of the articular capsule (*3*). A frayed superficial part of the capsule is indicated by *1,* and the frayed deltoid portion of the subdeltoid bursa, by *5.* Not all longitudinal trabeculae of the capsule were numbered; a very narrow one lies between *1* and *2.*

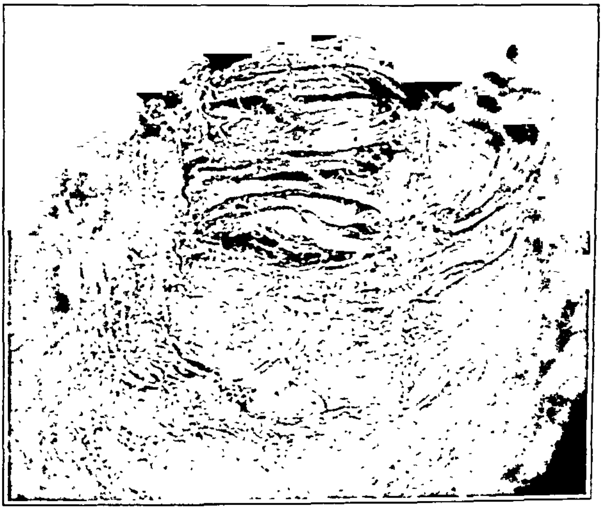

Fig. 6.—A left shoulder joint with a similarly frayed and trabeculated capsule and tendon of the supraspinatus. It should be noted that all the trabeculae are longitudinal in direction with respect to the tendon of the supraspinatus.

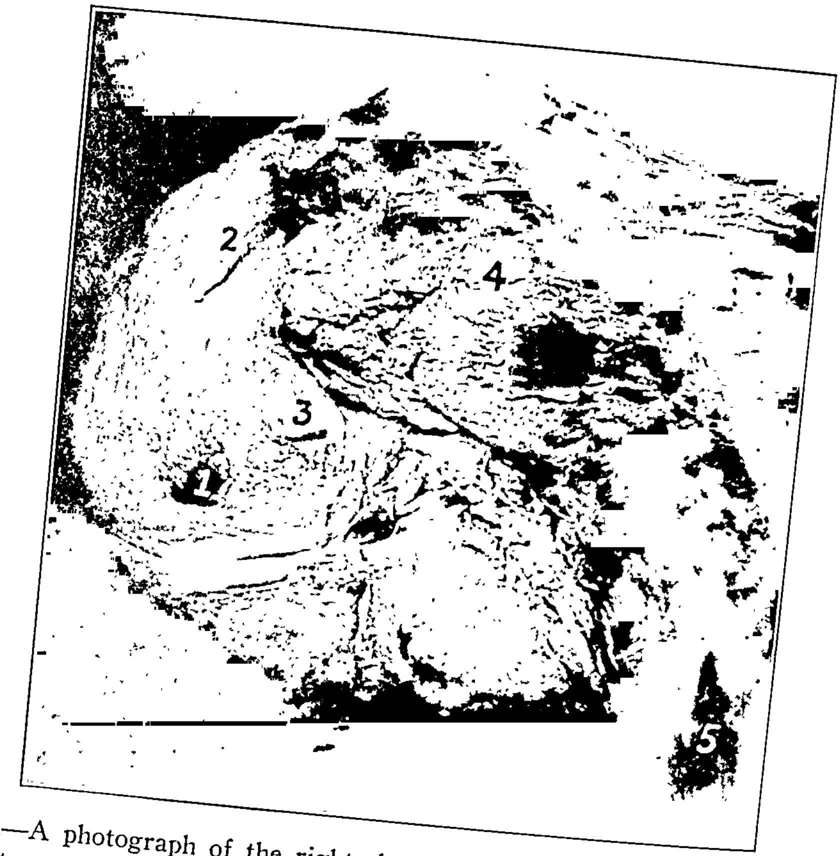

Fig. 7.—A photograph of the right shoulder from in front and above. Longitudinal slits are seen at *2* and *3* on either side of an unaffected tendon of the supraspinatus. A large, irregularly shaped hole is seen at *1*. The acromion is indicated by *4* and the clavicle by *5*.

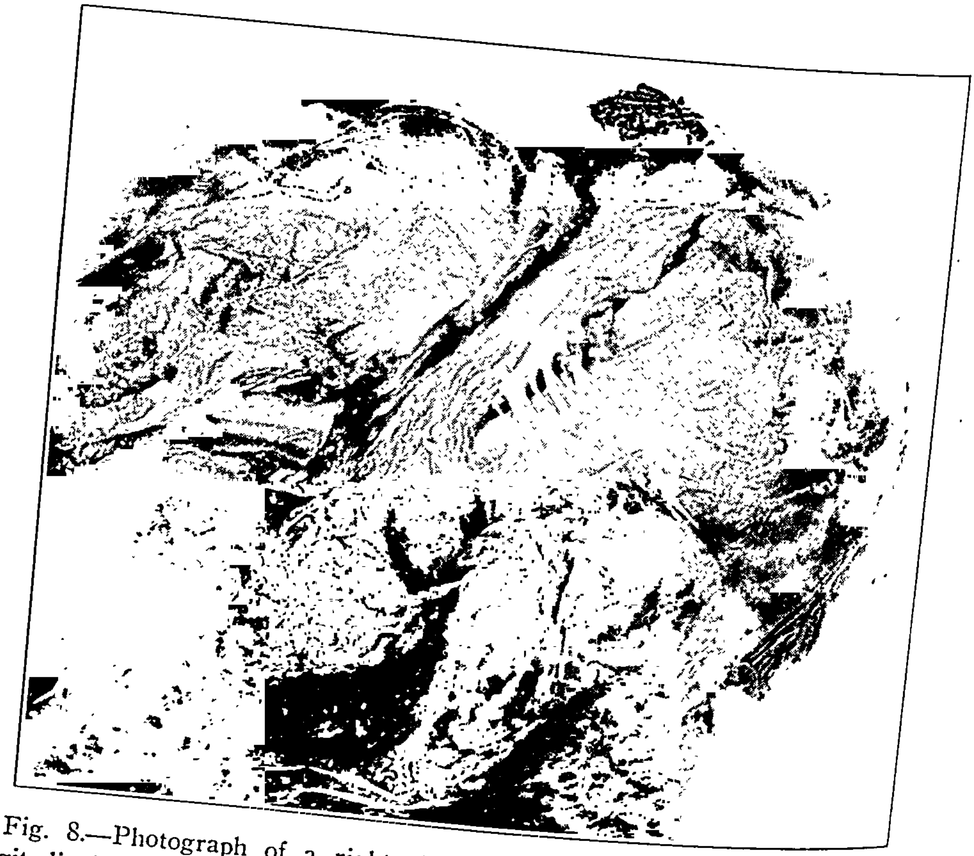

Fig. 8.—Photograph of a right shoulder in a similar view showing a long longitudinal slit at the smooth anterior border of an unaffected supraspinatus tendon. Fine, narrow trabeculae, remnants of the superficial layer of the articular capsule, are seen bridging the slit.

exposed to similar wear, for under such conditions it must act vicariously for the destroyed portion of the capsule. A large part of the midsection of the proximal portion of the deltoid muscle may be destroyed completely. Whenever this happens, only the skin, the subcutaneous tissues, the superficial and deep fasciae and the fused sheaths of the deltoid muscle remain as a cover for the joint, and it would seem that it should be possible to diagnose such a condition in life. Such extensive destruction must be relatively rare, however, for I have seen but a single example in about a thousand bodies and have learned of no other instance, although fraying of a portion of the under surface of the deltoid muscle is not uncommon.

CHANGES IN THE LONG TENDON OF THE BICEPS

It is interesting that the intra-articular portion of the long tendon of the biceps muscle may be destroyed completely without destruction of the articular capsule and without the presence of pathologic changes anywhere in or about the joint. The tendon usually shows wear from beneath, but evidences of this not infrequently are present also on its upper surface. Erosion along the lateral margins may be due to a disproportion in width between the more proximal, intra-articular, portion of the tendon, which often is much wider, and the lateral walls of the bicipital sulcus, although it is more commonly due to contact with slight irregularities on the walls of the sulcus, apparently the result of periosteal injury from wear. Fraying of the under surface of the tendon usually results from contact with the cartilaginous margin of the head of the humerus, with the supratubercular ridge (see fig. 3, Meyer [2]), when present, or with slight irregularities on the floor of the sulcus, representing reactions to wear, or from contact with the lesser tuberosity in cases of partial or total dislocation. Whenever the relatively rough surface of the lesser tuberosity comes into contact with this tendon after partial or total forward dislocation of it and detachment of the capsular attachment between the lesser tuberosity and the sulcus, destruction of the tendon is greatly facilitated, but whenever it remains in a capsular sling it may become completely dislocated without grossly evident wear.

It is surprising and also very significant that the tendon of the supraspinatus and the long tendon may reach paper thinness without rupturing. Indeed, it is not at all uncommon to encounter long tendons of which so small a fasciculus remains that it cannot bear a weight of 10 pounds.[3] Yet I have never seen a case of acute rupture in the dissecting room, and I have never been able to find more than a proximal trace of the relatively long intra-articular portion of this tendon. This probably is due to division of it long before death and to destruction of the proximal portion by attrition and lysis.

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[2] Meyer, A. W.: Spontaneous Dislocation and Destruction of Tendon of the Long Head of Biceps Brachii; Fifty-Nine Instances, Arch. Surg. **17**:493-506 (Sept.) 1928.

[3] This no doubt is accounted for by the fact that secondary attachments are formed before the tendon is completely divided.

An excellent specimen showing wear on both surfaces of the long tendon is represented in figure 9, which is a photograph of the intra-articular portion from the right shoulder of a man whose left tendon was wholly unaffected. The wear on the superficial or upper surface and on the anterior margin of this long tendon was due to contact with the overlying capsule—the so-called transverse humeral ligament.[4] Wear on its under surface was from contact with a supratubercular ridge in the region of the lesser tuberosity. Since this tendon was undergoing spontaneous dislocation, its anterior margin and its upper surface were forced against the overlying capsular attachment, its dislocation being facilitated by the presence of a supratubercular ridge, which forced it

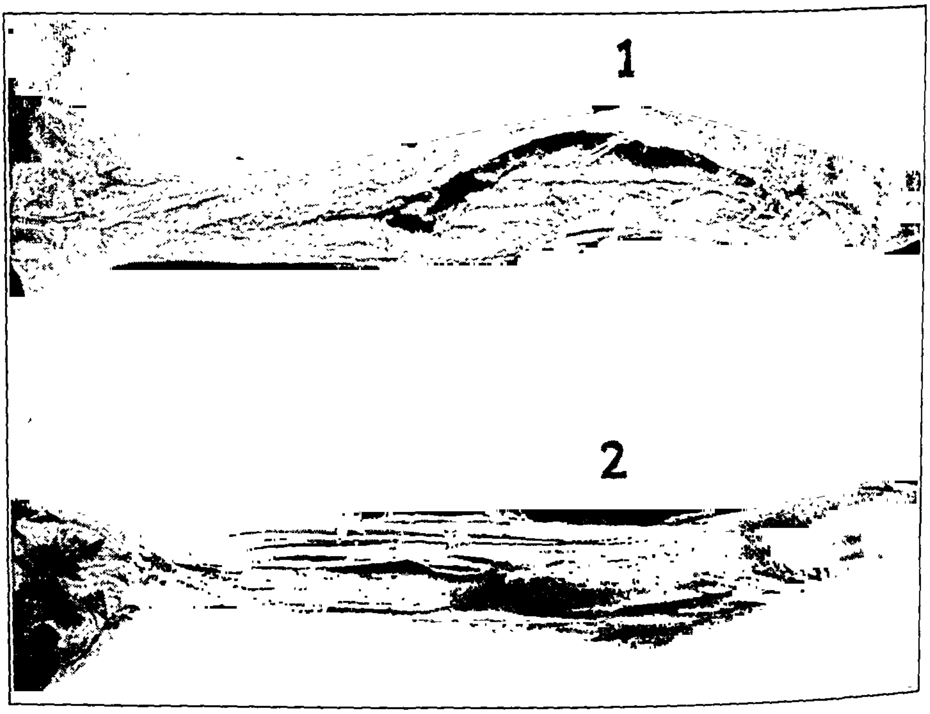

Fig. 9.—Right long tendon taken from a joint showing no evidences of disease. Both surfaces are markedly, though superficially, frayed. The proximal ends are to the left. Note the longitudinal fasciculation of the tendon, the detached synovial sheath and the fraying on both surfaces and the anterior margin to near the supraglenoid attachment.

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[4] In cases of destruction of the overlying capsule, the superficial surface of the long tendon may also be worn by contact with the deep surface of the coraco-acromial ligament.

upward from the sulcus as well as forward. Under these circumstances, the tendon has to act as a wedge during its dislocation forward from the groove.

Whenever a portion of a tendon is deprived of the protective effect of the covering articular capsule and of its own sheath, its nutrition must of necessity be interfered with very seriously. At any rate, the portions of tendons so denuded become separated into longitudinal fasciculi of varying caliber. These readily become divided by contact with the cartilaginous margin of the head of the humerus or other surfaces of contact and may then easily be mistaken for portions of the tendon which were ruptured. This fasciculation of tendons is especially common on the under surface of the tendon of the subscapularis and of the tendons of the supraspinatus and the infraspinatus, but it occurs also on the upper or superficial portion of the tendon of the subscapularis and especially on the under surface of the long tendon of the biceps. I have encountered it in many places, even where the tendon of the peroneus longus glides on the facet of the cuboid bone, as shown in figure 10.

CHANGES IN THE TENDON OF THE SUPRASPINATUS

Fraying, thinning and final destruction of a part or the whole of the width and the thickness of the distal portion of the tendon of the supraspinatus as a rule are effected largely or wholly from without or above, while the tendons of the long head of the biceps and the tendons of the subscapularis and the infraspinatus usually are involved from within or beneath. However, the superficial portion of the tendon of the subscapularis may become fasciculated from movement against the under surface of a partially or wholly dislocated tendon of the biceps, after the protecting and overlying portion of the articular capsule has been detached or stretched to form a sling. Hence both surfaces of this tendon, like those of the biceps and of the supraspinatus, may suffer simultaneously, even if not equally.

Dislocation medially (forward) of the long tendon of the biceps may take place without detachment of the adjacent portion of the articular capsule, for the latter may merely stretch and form a sling which can glide on the long tendon in movements of the arm and protect it from contact with the underlying cartilage or bone. If the tendon of the subscapularis likewise retains its attachment, the long tendon may hence become dislocated completely without suffering much wear. But just as soon as the articular capsule becomes detached medially (anteriorly) and capitularly to the lesser tuberosity, dislocation of the intra-articular portion of the long tendon can begin; and it not infrequently becomes complete, although still in its normal position in the rest of the bicipital sulcus. Whenever the roof of the intertubercular portion of the sulcus yields, the long tendon can gradually become dislocated forward over the lesser tuberosity and lie on the tendon of the subscapularis or on the lesser tuberosity itself, in case of detachment of the latter tendon from it. In the cases of the most maximal dislocation of the long tendon which I have seen, the more distal portion always lay in its normal position. This it does not leave either laterally or medially because of the firm attachment of the great tendons on either side and because of the directions of pull.

CHANGES IN CARTILAGES

The central area of the articular cartilage of the head of the humerus not infrequently also shows the effect of wear, but this does not imply that the central portion of the cartilage on the glenoid cavity must show the same effect, for a small portion of it is composed of fibroid instead of hyaline cartilage. The hyaline cartilage on the head of the humerus just proximal to the greater tuberosity may also be affected whenever it comes into direct contact with the under surface of the acromion, and it is in this region of the greater tuberosity and on the under surface of the acromion that polishing and eburnation are generally observed first. These polished areas seldom are congruent, however, and that is what one should expect. One may be several square centimeters in area, while the other coapted with it may be so small as to be scarcely noticeable, just as one can deface a large area with a fine diamond point.

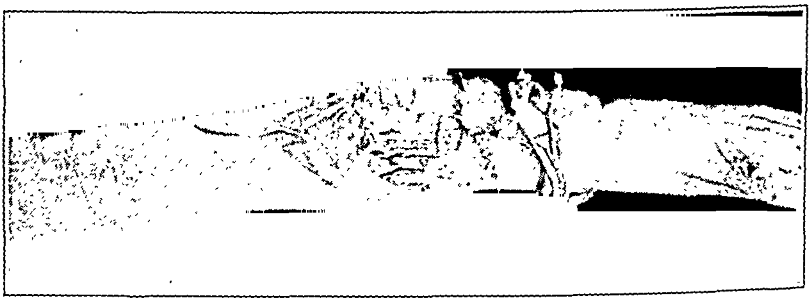

Fig. 10.—Right peroneus longus tendon seen from below with the distal extremity to the right. Note the detached synovial sheath near both extremities of the worn portion and the depth of the wear. The facet on the cuboid bone with which this worn area was in contact was normal in all respects and so were the rest of this tendon and its synovial sheath.

The superficial membranoid layer of hyaline articular cartilage, which the older anatomists mistook for synovial membrane and which occasionally still is regarded so today, becomes frayed first. However, the thicker, uncalcified underlying layer not infrequently is chipped off from the underlying calcified layer in considerable areas over the head of the humerus. Whenever the latter becomes detached, the underlying compacta is exposed, and polishing and eburnation can begin as soon as this area comes into contact with a similarly denuded area on the scapula or with an ossific plaque or nodule in the articular capsule. I have seen a number of such ossifications a centimeter or more in size which were exquisitely polished from contact with the head or the tuberosities of the humerus. Such nodules may also be polished on the external surface whenever they are in an area of the capsule which will permit them to come into contact with the acromion or the coracoid process.

Quite frequently the inferior acromioclavicular ligament and the respective portion of the capsule contain defects varying from small gaps to complete destruction of this portion of the capsule. Since shoulders with such defects which happened to come to my attention first also contained large defects in the upper portions of the humeroscapular articulations with complete division of the tendons of the supraspinatus muscle and partial destruction of the acromioclavicular ligaments, I had concluded that these defects in the acromioclavicular capsules and ligaments were due to contact with the heads of the humeri and the adjacent regions of the greater tuberosities. Of late I have observed a number of defects which cannot be accounted for in this way, however. In the latter instances the defects in the acromioclavicular capsule had been produced from above by contact with the inferior surface of the distal extremity of the clavicle and perhaps to some degree also by contact with the similar margin of the articular facet of the acromion. The lesion is surprisingly common and may be accompanied, preceded or followed, by the formation of a synovial bursa below this articulation in the connective tissue and fat overlying this portion of the supraspinatus muscle. Sometimes the musculotendinous junction is extensively fasciculated and frayed for an extent of several centimeters. Examples of these lesions with illustrations can be found in a forthcoming article on "Use Destruction in the Human Body," in *California and Western Medicine*.

Although in the long course of the gradual production of such lesions as these, slight hemorrhage may occur whenever a weakened structure suddenly yields, I have never encountered evidences of it. Thickened bursal walls and some coagulum were discovered only a few times in almost a thousand bodies, and effusions and adhesions were never seen. Gross and microscopic examination of a considerable series of specimens yielded no evidence of the presence of chronic inflammation.

Short distal stumps of the tendon of the supraspinatus muscle and of the adjacent capsule and transverse rents in the latter were seen only a few times. The defects and the fasciculations usually extended in the direction of pull, and the earliest capsular and tendinous defects always were bounded by smooth, attenuated borders of capsule and tendon instead of by frazzled, thickened borders. Since, as shown in figures 7 and 8, longitudinal capsular defects also occur in the ventral (anterior) intertendinous portion of the capsule and broader defects also dorsally (posteriorly) beneath wholly uninjured tendons of infraspinatus muscles, these defects manifestly cannot be due to the rupture of associated tendons. The same thing is true of the fraying on the internal surface of the capsule opposite the cartilaginous margin of the head of the humerus and on the inner margin of the glenoid fibrocartilage, where fraying is practically universal. Rarely these cartilages may be nearly or wholly destroyed for a part of their extent.

The occasional presence of ossific nodules in different places in the upper half of the joint capsule, in the tendon of the infraspinatus muscle and even in the coraco-acromial ligament suggests that sudden trauma, greater in intensity than that which can be attributed to wear, may have been responsible for their production. That can readily be granted, for what laborer could be so fortunate as to escape sudden trauma to the shoulder during decades of an active life? The frank recognition of this fact surely cannot negate the overwhelming evidence against the assumption that all the lesions here considered result in this way or are the product of disease.

RUPTURE OF THE TENDON OF THE SUPRASPINATUS

Although Codman[5] (p. 120) thought weakness of the tendon of the supraspinatus muscle is due to its evolutionary history and spoke (p. 144) of "the strain on this little tendon," he nevertheless said (p. 150) that the insertion of this tendon is ¾ inch (1.9 cm.) long. On the basis of the best calculations available, the more prevalent form of tendon of the supraspinatus has a tensile strength many times that of its muscle belly. According to Triepel,[6] Fick,[7] Cronkite[8] and investigators mentioned by them, a supraspinatus tendon ¾ inch (1.9 cm.) wide and only 2 mm. thick could bear an estimated pull of over 700 pounds (318 Kg.), and one 3 mm. thick could bear a pull of over 1,000 pounds (454 Kg.). The muscle belly of the supraspinatus, on the other hand, even when it is large, has an estimated maximum strength of only 170.9 pounds (77 Kg.). Since the tendon of the supraspinatus muscle with the included capsule often is considerably thicker than 3 mm., the true disproportion between the strength of the unworn tendon and that of the muscle is greater than the foregoing estimates indicate. This alone makes rupture of a sound normal tendon by active muscle pull alone doubtful, and even if such a relationship did not exist and the tendon were relatively too weak and then were torn in part only, thus reducing its ability to withstand the next maximal muscular contraction, it then should yield suddenly. Moreover, since the worn supraspinatus tendon always becomes gradually thinner toward the point of its insertion, where it may be of membranoid thinness without perforation, it follows that all such tendons should have yielded earlier to sudden muscle pull and that they should contain transverse instead of longitudinal tears and trabeculae. And how could one entertain the belief that contraction of the subscapularis can avulse the large tubercular portion of the tendon, always leaving the relatively small diaphysial attachment intact, or that the greater upper part of the insertion of the infraspinatus may likewise be detached and the small, weaker, lower portion always remain unruptured? Yet this was always the case in my observations. Sudden rupture of the sound supraspinatus tendon should leave normally thick or thicker ragged, blunt ends, and sudden detachment of the tendon from its insertion should leave the fractured or intact border of the greater tuberosity protruding to impinge suddenly against the acromion in abduction of the arm. Since the cervical sulcus of the humerus sometimes is deep here and the tuberosity very prominent, such a sequence of events certainly would make itself felt severely during life and would not escape the attention of the clinician. Gradual erosion of the tendon, on the other hand, whether from within or from without, gives atrophy an opportunity to produce its leveling and reducing effects, lowering the height of the greater tuberosity and thus rounding the contour of this region of the humerus. Any one sufficiently familiar with the changes in it and in the region of the lesser tuberosity is aware of the great reduction sometimes suffered, especially by the latter, after detachment of the tendon. The entire place of the lesser tuberosity sometimes is occupied by a smooth, sunken field and at other times by a somewhat rougher field than normal. Examination of the spongiosa beneath may reveal a large absorption cavity akin to Ward's triangle in the spongiosa of senile femurs (see fig. 1, Meyer [9]). I have never noticed equally marked atrophy of the spongiosa in the region of the greater tuberosity, but this may be due to the fact that since the latter continues to impinge against the under surface of the acromion, the underlying spongiosa is continually subjected to strains sufficient to preserve it from the marked atrophy of disuse to which that underlying the lesser tuberosity is subjected after detachment of the tendon of the subscapularis.

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[5] Codman, E. A.: The Shoulder: Rupture of the Supraspinatus Tendon and Other Lesions in or about the Subacromial Bursa, Boston, The Author, 1934.

[6] Triepel, Hermann: Einführung in die physikalische Anatomie, Wiesbaden, J. F. Bergmann, 1902-1908.

[7] Fick, Rudolf: Handbuch der Anatomie und Mechanik der Gelenke unter Berücksichtigung der bewegenden Muskeln, Jena, G. Fischer, 1910-1911, nos. 2 and 3; in von Bardeleben, K. H.: Die Anatomie des Menschen, Leipzig, B. G. Teubner, 1908, vol. 2, nos. 1 and 2.

[8] Cronkite, Alfred Eugene: The Tensile Strength of Human Tendons, Anat. Rec. **64**:173-186, 1936.

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[9] Meyer, A. W.: Unrecognized Occupational Destruction of the Tendon of the Long Head of the Biceps Brachii, Arch. Surg. 2:130-144 (Jan.) 1921.

THE QUESTION OF ATROPHY

I am aware of the fact that atrophy of the supraspinatus muscle has been emphasized as a diagnostic sign of rupture of its tendon, but I have been able to detect the presence of marked atrophy of it only a few times in cadavers. This applies likewise to the lateral belly of the biceps and to that of the subscapularis and of the infraspinatus. It appears to me that the absence of marked muscular atrophy, even in the presence of pronounced lesions in the tendons of these muscles, may be accounted for by the fact that the tendons are divided gradually, that the nerve supply of the muscles is left intact and that they hence can respond and continue to contract against some resistance. Moreover, it must not be overlooked that the long tendon of the biceps gradually obtains a secondary attachment in the region distal to the tuberosities, usually the lesser tuberosity, and that those of the subscapularis and infraspinatus never become wholly detached. The invariable presence of such a secondary attachment of the biceps, it seems to me, is adequate evidence that sudden rupture probably did not play a part in these cases, for were this so, considerable elongation of the brachial portion of the tendon should be common instead of very rare. Moreover, the invariable reattachment of this tendon at the same level on the humerus could not be accounted for. Reports of cases of acute rupture in which operative treatment was employed (Gilcreest[10]) confirm these conclusions. On the other hand, since the tendon must yield gradually when weakened by wear, it obtains a secondary attachment before it is completely divided.

I have never seen any evidences of the existence of osteitis in the region of the lesser tuberosity, as described by Béra,[11] and do not believe that it could be a factor in reducing the size of the lesser tuberosity and thus facilitate dislocation of the long tendon of the biceps. Chronic osteitis, unless suppurative, should not cause destruction of the bone, and as long as the ligamentous, capsular and tendinous attachments remain intact, dislocation of the long head is impossible. The following words from Béra's splendid thesis deserve repetition, however:

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[10] Gilcreest, Edgar Lorrington: (*a*) Rupture of Muscles and Tendons, Particularly Subcutaneous Rupture of the Biceps Flexor Cubiti, J. A. M. A. **84**:1819-1822 (June 13) 1925; (*b*) Two Cases of Spontaneous Rupture of the Long Head of the Biceps Flexor Cubiti, S. Clin. North America **6**:547-554, 1926; (*c*) Dislocation and Elongation of the Long Head of the Biceps Brachii: An Analysis of Six Cases, Tr. West. S. A. **44**:260-296, 1934.

[11] Béra, Albert: Du syndrome commun à la rupture, à la luxation et à l'élongation du tendon du long biceps, Thèse de Paris, no. 304, Paris, Jouve & Cie, 1911.

> *Les anomalies congénitales.*—Il est intéressant de faire remarquer que les anatomistes ont fréquemment cité des cas où la longue portion du biceps se fixait anormalement dans la coulisse bicipitale, sur les tubérosités humérales, sur la capsule de l'articulation de l'épaule (Dr. Le Double, *Variations du système musculaire de l'homme,* t. II). Il est permis de se demander si certains de ces faits ne rentrent pas dans le cadre de l'affection qui nous occupe; et si cette anomalie d'insertion n'est pas souvent l'effet secondaire d'un traumatisme plutôt que le résultat d'une malformation congénitale.—Ici encore, la perceptibilité du tendon bicipital au-dessous du bord deltoïdien, constatée sur le vivant ou sur le cadavre, permettrait de trancher la question [p. 48].
>
> Cette luxation primitive et isolée existe-t-elle en tant qu'affection franche et persistante, la chose est peu probable. Elle entraine non seulement l'ouverture de la coulisse bicipitale, mais encore la destruction de la capsule articulaire et du tendon du sus-épineux [p. 38].
>
> *Congenital Anomalies.*—It is interesting to note that anatomists have frequently cited cases in which the long head of the biceps muscle was abnormally fixed in the bicipital groove, on the humeral tuberosities or on the capsule of the joint of the shoulder (Dr. Le Double: Variations du système musculaire de l'homme, vol. 2). It is allowable to ask whether some of these facts do not enter into the picture of the disturbance of which we treat and whether this anomaly of insertion is not often the secondary effect of a traumatism rather than the result of a congenital malformation. Perception of the bicipital tendon below the deltoid border in the living subject or in the cadaver would allow one to decide the question [p. 48].
>
> That this primary and isolated luxation exists as a frank and persistent disturbance is improbable. It leads to not only the opening of the bicipital groove but also the destruction of the joint capsule and of the tendon of the supraspinatus muscle [p. 38].—Publisher's translation.

I have never seen a case of spontaneous dislocation of the long tendon dorsally over the greater tuberosity, and it seems to me that this is wholly precluded by normal anatomic conditions. All dislocations of the biceps tendon seen by me were forward dislocations, and I never saw any evidences that fractures or previous dislocations had been contributory factors in producing the lesions I am considering. However, that there may be such cases I gladly recognize.

Whenever the tendon of the long head is retracted into the brachium somewhat from yielding of the secondary attachments before, or from retraction of the tendon after, rupture of the weakened intra-articular portion, the brachial part of the tendon is longer, and marked asymmetry between the position of the two muscle bellies of the biceps necessarily results and is intensified whenever the lateral belly atrophies because of elongation of the tendon.

No one sufficiently familiar with the evidence present in cadavers with respect to these lesions of the shoulder and others present throughout the entire human body can have any doubt as to their significance. Indeed, the only phenomenon which still perplexes me is the exact manner of detachment of the subscapularis tendon from its insertion to the lesser tuberosity, for the middle portion of this tendon may be detached when the rest of it still remains attached by a peripheral ring of fine cylindric tendinous fasciculi, and complete detachment of the tendon from the lesser tuberosity may be present in cases of the developmental absence of the lateral belly of the biceps brachii. In some instances, too, only a few thin ribbon-like bands of tendon remain attached at intervals from above downward on this tuberosity. Such cases as these are rather puzzling, but they are that no matter what one may regard as causative factors in detachment of this tendon. Since atrophy of the tuberosity occurs in the areas of detachment of the tendon, it is possible that this absorption plays a rôle in the production of these anomalous detachments. Moreover, since the blood supply of tendons comes almost wholly from without, it follows that the destruction of the enveloping sheath must affect the firmness of attachment of the tendon in the course of time. Sharp or irregular portions of the cartilaginous margin of the head of the humerus, the osteogenetic reactions evoked in the traumatized periosteum and the absorption of cartilage no longer subjected to pressure from the tendon of the long head, all may be factors in the production of these detachments of the tendon of the subscapularis. Although the lesser tuberosity sometimes is normal in size and smoothness and covered with a thickened periosteum after the detachment of this portion of the insertion of the tendon of the subscapularis, it may be decidedly pitted and covered by an exceedingly thin periosteum or show little evidence of atrophy and be roughened by numerous low exostoses.

I have often wondered whether dislocations of the shoulder are not commoner in cases of maximal destruction from attrition and whether in some cases habitual dislocation may not be due to it, but I never have encountered such a condition in the dissecting room. However, since the stability of the shoulder joint depends so largely on muscles and tendons, it would seem that partial or complete destruction of the tendon of the supraspinatus and partial destruction of that of the infraspinatus accompanied by loss of the tubercular attachment of the subscapularis tendon must seriously reduce the stability of the joint even if not markedly affect its functional activity.

It seems that it should be possible to notice the presence of bony contacts in all cases in which this has become possible in consequence of capsular and tendinous or cartilaginous attrition. From my experience in auscultation of various supposedly normal articulations during movements which required no special strain, I am led to believe that more can be made of this method of examination. It would also seem that the gap between the acromion and the head of the humerus indicated in roentgenograms must be reduced whenever the capsule or the articular cartilage on the head of the humerus or both are destroyed. Under the relaxation of deep general anesthesia, it should also be possible to produce a tap by forcing the head of the humerus against the lower surface of the acromion in all cases of large capsular defects. Although functional disabilities may be very misleading, some of them nevertheless must be suggestive with regard to both the extent and the character of the lesions present.

It is true that the literature on conditions of the shoulder plainly suggests that some of the symptoms, signs and disabilities accompanying the trauma of attrition have been attributed to dislocation, rheumatic arthritis, arthritis deformans, rupture, neuritis, periarthritis, bursitis, tendinitis, senile necrosis, wear following disease and the effect of sudden motion, but that is an inference not based on personal knowledge of the cases concerned. The implication is not, to be sure, that none of the conditions mentioned can cause changes in and about the shoulder joint but that there may be profound changes without the presence of any of the foregoing conditions except that of wear.

REVIEW OF LITERATURE

Any one who has dissected a series of human bodies or has carefully observed their dissection must have encountered some, even if not all, of the foregoing lesions. Indeed, there is ample evidence in the medical literature to show that occasional observers have tried to explain very similar even if not identical phenomena, although Smith[12] thought that they have been "entirely overlooked . . . from inadvertency or other causes . . . in the ordinary dissection of bodies." During the dissection of forty bodies, Smith observed seven instances of destruction of the upper part of the capsule of the shoulder joint, destruction of part of the long tendon of the biceps and detachment of the tendon of the subscapularis and concluded that they were due to external factors such as a blow or fall, but he thoughtfully added:

> It is a curious fact, that in two instances both joints of the same individual should have presented nearly similar appearances, and that the same cause should probably have produced exactly similar results [p. 222].

According to Smith:

> The separation of the tendon of the subscapularis muscle from the lesser tubercle, (excepting in one case), where it was only partially torn away, may

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[12] Smith, John G.: Pathological Appearances of Seven Cases of Injury of the Shoulder Joints, with Remarks, Quart. Periscope, Am. J. M. Sc. **16**:219-224 (May) 1835; London M. Gaz. **14**:280-285, 1834.

> be looked upon as the common result of the accident which produced these appearances; not so, however, with the tendons of the supra and infra-spinatus, and the teres minor muscles, from the greater tubercle, which appear to be more uncertain. In two instances all three tendons were torn away; in three cases only the tendon of the supra-spinatus; and in the remaining two cases, the whole of the tendons preserved their natural attachments [p. 222].

Callaway,[13] like Smith, stated explicitly that what he observed were cases of traumatic rupture and dislocation of the tendon of the long head of the biceps muscle, and Rapp,[14] who used the significant and appropriate word *Usur* in connection with lesions of the tendon of the long head of the biceps and who also represented the proximal portion of the torn tendon with a brushlike, free extremity as shown in figure 11, regarded this as due to growth after injury and concluded that luxations, disturbance of the circulation in the tendon sheath and inflammation may cause changes in the normal tendon of the biceps such as he encountered and the significance of which he was considering.

One of the historically most interesting and significant discussions of conditions in the shoulder is presented in an article by Robert Adams,[15] which appeared in Todd's "Cyclopaedia of Anatomy and Physiology." Under the subhead of "chronic rheumatic arthritis of the shoulder joint," a "slow chronic disease" which "itself never causes death," Adams described many lesions such as those considered here, including destruction of the upper portion of the articular capsule; division, dislocation and reattachment of the long head of the biceps muscle; local destruction of the articular cartilages; destruction of the deeper portion of the capsule of the acromioclavicular articulation, and polishing of the head and tuberosities of the humerus and of the under surfaces of the acromial and coracoid processes. However, Adams also reported and included enlargement of the bones of the shoulder; thickening and enlargement of the articular capsule with adhesions to the acromion, coracoid process and the head of the humerus; frequent complete transverse division of the acromion within an inch of its extremity; effusions into the articular capsule with the presence of osseous fragments, and dislocation of the head of the humerus upward beyond the level of the clavicle and acromion and "completely backward on the dorsum of the scapula." The illustrations accompanying Adams' article show the presence of extensive articular exostoses and pronounced osseous extensions, such as are seen in so-called arthritis or arthrosis deformans. He emphasized the presence of "rheumatic arthritis" in practically all joints in his cases and believed that the case of Cruveilhier, in which ". . . the external extremity of the clavicle and the neighboring part of the acromion were in a great part destroyed," likewise belonged in the same category. Adams thought that "absorption" of the articular cartilages, both hyaline and fibroid, was effected by contact with capsular fimbria or so-called synovial villi, but recognized the presence of friction under such pathologic conditions.

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[13] Callaway, Thomas: A Dissertation upon Dislocations and Fractures of the Clavicle and Shoulder-Joint, Jacksonian Prize Essay for 1846, London, S. Highley, 1849, p. 178; reviewed, Lancet **2**:400-401, 1849.

[14] Rapp, Hermann: Ueber die Usur der Sehne des langen Kopfes vom M. Biceps brachii, Dissert., Tübingen, 1866.

[15] Adams, Robert: Shoulder Joint, in Todd, R. B.: Cyclopaedia of Anatomy and Physiology, London, Longman [and others], 1852, vol. 4, pp. 571-621. Although this volume appeared in 1852, the text plainly implies that the article was written in 1848.

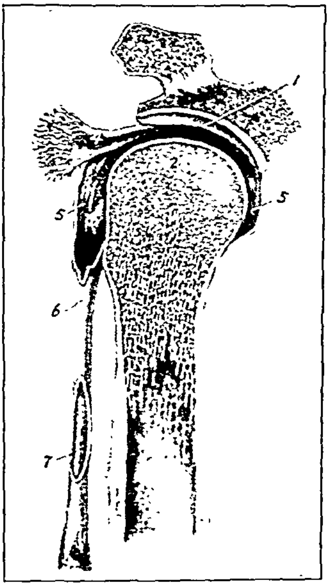

Fig. 11.—Sagittal section of a right shoulder. The glenoid cavity of the scapula is indicated by *1,* the head of the humerus by *2,* the tear and partly an outgrowth of the upper end of the tendon of the long head of the biceps by *3,* the long head of the biceps by *4,* the synovial capsule of the shoulder by *5* and the tendon sheath of the long tendon of the biceps by *6.* The last-mentioned structure contains a sequestrum of the original tendon, indicated by *7.* Those familiar with attrition effects will recognize that *3* is due neither to tear nor to growth. (After Rapp.[14])

He thought, however, that "no doubt some few cases of chronic rheumatic arthritis of the shoulder joint in the living and in the dead have been mistaken for *partial dislocation of the head of the humerus, the results of accident* . . . " He was ". . . convinced that all these phenomena combined should by no means be considered as proof of any accident having occurred to produce them; but, on the contrary, should be looked upon as the usual result of chronic rheumatic arthritis of the shoulder." He emphasized that in 1836 he had called attention to the fact that appearances delineated by Sir Astley Cooper in his treatise on "Fractures and Dislocations" corresponded exactly to the appearances found in the cases of "chronic rheumatic arthritis" and that all his subsequent experience "amply confirmed" this opinion, adding that he ". . . thought it necessary to enter into this subject thus minutely, because we are convinced that, up to the present hour, these remarkable appearances, when met with, have been misunderstood even by some of the most intelligent anatomists and physicians."

In the well known "Treatise on the Human Skeleton Including the Joints" by Humphry,[16] some similar lesions were likewise mentioned, for when considering defects in the long tendon of the biceps, Humphry wrote:

> The rent most often happens about half an inch from its glenoid attachment; and is most frequent in elderly persons, in whom the tendon becomes thin, in whom the synovial fluid is rather scanty, and in whom other changes, attendants on chronic rheumatism, are likely to be in progress.

I do not know of any evidence in support of the assumption that tendons become thin and synovia scanty, under the conditions concerned here, but Humphry very significantly said:

> Under these circumstances there can be no doubt that the tendon sometimes becomes *worn through* by the friction of the head of the humerus upon it; and I quite agree with the writer in the Cyclopedia of Anatomy [Adams], that many of the specimens, in which the biceps tendon stops short in the bicipital groove, or becomes lost in the capsule of the joint, are to be attributed, not to rupture of the tendon, but to the continued effects of chronic rheumatism, originating in an accident, or commencing spontaneously [p. 415].

It is noteworthy that Humphry added the following in a footnote:

> It would appear, from some dissections of the shoulder-joint described by Mr. J. G. Smith, *Medical Gazette,* XIV. p. 280, that, not only may the tendon of the biceps be worn through, but that the capsular ligament and the tendons of the supra- and infra-spinatus muscles may undergo the same change, and the sub-deltoid bursa thus become opened into the cavity of the joint. In several of the cases mentioned the sub-scapularis tendon was more or less detached from the lesser tubercle. Mr. Smith regards these changes as the result of accident; but several other points in the state of the joints, and the existence of similar conditions in both shoulders of the same person, render it more probable that they were the gradual result of friction and chronic rheumatism.

It is of interest in this connection to recall that Sir W. Arbuthnot Lane[17] thought ". . . that the pressure which in elderly subjects

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15. Humphry, George Murray: A Treatise on the Human Skeleton Including the Joints, Cambridge, Macmillan & Co., 1858.

17. Lane, W. Arbuthnot: A Remarkable Example of the Manner in Which Pressure-Changes in the Skeleton May Reveal the Labour-History of the Individual, J. Anat. & Physiol. **21**:385-406, 1887.

or in those of low vitality destroys the articular cartilage and the subjacent bone, rendering the latter eburnated, and determining the formation of additamentary bones, produces in a young subject a similar alteration in the form of the articular surface, without affecting the vitality or continuity of its cartilaginous covering" (p. 386). He thought that ". . . pressure-changes in the skeleton may enable us to detect the habits and labour-history of the individual" (p. 386) and concluded regarding one case that "during the whole of his active life this man had been continually occupied in shovelling some material which was very coarse . . ." (p. 398). Sir Arbuthnot also spoke of a case in which ". . . the glenoid ligament was separated completely from the upper third of the margin of the glenoid cavity, being connected to it indirectly by a thin membrane. The upper part of the glenoid cavity was slightly increased in area. The cartilage covering the lower part had been converted into synovial membrane and areolar tissue . . " (p. 388). He attributed these things to an "upward displacement of the head of the humerus which ensues in old age. . . ." (p. 388), but he recognized that bone may be removed as a result of "friction and pressure" and thought that pressure from the radial head of the humerus on the head of the radius may cause polishing and eburnation (p. 389). He offered this explanation also for perforated or wholly destroyed articular cartilage at the distal extremity of the ulna (p. 390) and believed that he had "shown that constant pressure exerted by the inferior articular processes of the 4th lumbar vertebra, and by the superior articular processes of the sacrum upon that portion of the arch of the 5th lumbar vertebra which lies between their extremities, may cause its partial or complete section" (p. 398). After considerable discussion of this matter, Lane referred to two cases of this anomaly reported by Professor Neugebauer, which the latter said were very puzzling and which he ascribed to congenital causes (p. 400). Although Lane also referred to an article by Sir W. Turner in which the latter described "several cases of want of union of the neural arch with the body of the 5th lumbar vertebra, which he ascribes to imperfect development" (p. 401), Lane nevertheless held to his opinion as to the origin of these anomalies and said ". . . *that the causation of the condition is pressure and not fracture, or a non-union of bony centres*" (p. 401).

These quotations pointedly reveal the significance of the older literature, in which a fall, blow, fracture, dislocation or disease, especially arthritis, is usually assigned as cause for the lesions encountered. It is largely for this reason that I have not discussed that literature fully, for it ill becomes one who did not even see the cases described by others to question the correctness of their interpretations. A fine summary of the extensive older literature is given by Gilcreest.[10c]

Codman, who has given so much attention to painful shoulders, thought that a hole in the humeroscapular capsule might close completely and stated [18] that he put a good many silk "sutures à-distance" between the separated ruptured ends of a supraspinatus tendon, because ". . . it seemed possible for repair to take place along the silk sutures." No one will deny that a rupture in a normal capsule or tendon may heal provided the torn ends are in direct or indirect apposition and are put at rest immediately, but Dr. Codman stated that he never operated in any case until three weeks after rupture, and since the period given apparently was inferred there is no assurance that it may not have been three months after. Moreover, I infer that he believes that defects which are the result of wear, such as I am considering here, also may heal, for he said [5] (p. 86) that the triangular defects in the supraspinatus tendon always become rounded, as does a defect in the epithelium of the skin, "before it heals" and that incomplete ruptures (those in which the rent in the tendon is from ¼ to ½ inch [0.6 to 1.3 cm.] in length) will heal of themselves. Codman had also suggested earlier that clipping away the "inflamed" bursa over the ruptured tendon would cause satisfactory healing, but he [5] later doubted this (p. 131).

Wilson [19] considered only cases of complete rupture of the supraspinatus tendon with gaps up to "2½ inches in diameter." [!] He spoke of the presence of "fibrillation of the tendon and shredding with the formation of irregular tabs of tissue, sometimes calcified," and "occasionally fibrillation" of the articular cartilage on the head of the humerus as being most evident in patients in whom the longest time had elapsed since injury. Wilson found no pathologic changes present at the time of operation but said that the greater tuberosity is usually "bare" of tissue. If so, it follows that the distal stub of the ruptured tendon must have been completely resorbed in the interval between the accident and the operation, and if the greater tuberosity really was completely bare, it also is necessary to account for the absence of periosteum, which cannot be attributed to atrophy. On referring to some lesions of the shoulder reported by me and the suggested explanation for them, Wilson correctly said that "Most of his investigations have been made on dissecting room subjects," but he nevertheless added that these ". . . must have been cases of rupture of the supraspinatus tendon." [!]

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18. Codman E. A.: Complete Rupture of the Supraspinatus Tendon: Operative Treatment with Report of Two Successful Cases, Boston M. & S. J. **164**:708-710, 1911.

19. Wilson, Philip D.: Complete Rupture of the Supraspinatus Tendon, J. A. M. A. **96**:433-439 (Feb. 7) 1931.

Although Keyes[20] found almost complete obliteration of the subdeltoid bursa by fibrous adhesions which "resembled" those "in the peritoneal cavity, particularly in the pelvis of the female," and mentioned the presence of hypertrophic bony changes on the greater tuberosity and the adjacent regions, of deposits of calcium in the supraspinatus tendon, of increased fragility of the bone of the greater tubercle and of erosion of the articular surface of the humerus, he nevertheless emphasized that fraying of the tendon of the long head was not observed and that the tendon was intact in every instance, but in 1933 he[21] said that all his cases "were associated with a certain amount of tendon fraying and bony irregularity" and assured readers that "this description of one lesion covers the main features of all the other . . ." of a series of fourteen of seventy-two cadavers, or nineteen of one hundred and forty-two shoulders. A larger series of observations would undoubtedly have revealed greater variations among them.

Keyes also said, in 1933, that the tendon of the supraspinatus muscle "during the terminal half of its course [6 cm. according to Keyes] . . . is inseparable from the joint capsule," and that "its two borders may be distinguished from the adjoining borders of the tendon of the infraspinatus and subscapularis only with some difficulty. . . ." He added that rupture of the supraspinatus tendon "is related to subdeltoid or subacromial bursitis;" that the lesions considered by him were due to "some process . . . which progressed with years, gradually causing degeneration first of the floor of the subacromial bursa, then wearing through the tendon at its insertion into the greater tubercle, and finally causing a perforation or rupture of the tendon." However, in 1935 Keyes thought that the lesions were "traumatic and degenerative in nature" and that "age, long use, and trauma seemed the chief causative factors," although "alterations in tissue growth and metabolism were believed to act locally . . . ." He added that infection caused the changes seen in few of these shoulders. Keyes also reported the absence of atrophy of the supraspinatus muscle "even when a large rupture [up to 2.2 cm. wide by 3.5 cm. long] was present in its tendon . . . ."

Any one who has microscopically or even macroscopically examined the borders of the capsular defects I am considering must realize that spontaneous healing is absolutely out of the question, no matter what the size of the defect or the degree of use of the arm, for in order that healing may occur it is necessary not only that the edges of the defect be freshened and brought together but that the structures be put at rest. The mere presence of fluid or even of a coagulum between the widely separated ends of tendons divided by attrition weeks and months previously would not evoke or facilitate the least reparation and the startling suggestion that such reparation might occur along silk sutures between the widely separated ends of a tendon or capsule does not seem to rest on a sound basis.

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[20] Keyes, E. Lawrence: Anatomical Observations on Senile Changes in the Shoulder, J. Bone & Joint Surg. **17**:953-960, 1935.

[21] Keyes, E. Lawrence: Observations on Rupture of the Supraspinatus Tendon, Based upon a Study of Seventy-Three Cadavers, Ann. Surg. **97**:849-856, 1933.

I am reminded that Codman and Akerson,[22] writing on "The Pathology Associated with Rupture of the Supraspinatus Tendon," said that it is the usual cause of traumatic subacromial (subdeltoid) bursitis. I am at present writing a book to support this contention [p. 353]. . . . The large number of bilateral cases (fourteen) found at autopsy speaks against traumatism and in favor of some form of slow necrotic destruction" [p. 356]. It is important to note that Codman and Akerson apparently found no pathologic condition responsible for the alleged rupture of the tendon of the supraspinatus, and since bursitis is assumed to follow its rupture it manifestly cannot be a factor in its production. The only other pathologic process postulated is a "slow necrotic destruction" for the occurrence of which Codman and Akerson seem to have found no postmortem evidence except the presence of alleged rupture which the necrotic changes were supposed to cause.

It is important to note that Codman and Akerson gained their information on cadavers through "a cut . . . made on the anterior aspect of the shoulder-joint from the acromioclavicular articulation downward for about two inches" (p. 352). Any one who has followed careful dissections of the shoulder will recognize how inadequate such a method of postmortem examination is for revealing the true conditions in the joint. I admit that some one may examine a single shoulder thoroughly and come to a correct conclusion regarding the condition but scarcely on evidence obtained from inspection through a 2 inch (5 cm.) incision at autopsy.

I am wholly at a loss to understand how these authors could hold that "a purely anatomic argument against Doctor Meyer's theory is that the impingement of the head of the humerus on the lower surface of the acromion does not occur in the normal individual" (p. 357), for I certainly implied nothing of the sort. It does not require a lifetime in the dissecting room to apprise one of the fact that the head of the humerus is not in direct contact with the acromion when the joint capsule is intact! Moreover, the two sentences which follow the one just quoted are equally perplexing and unintelligible, for Codman and Akerson wrote: "The friction at this point is taken up by the outer side of the tuberosity which is covered with the lower surface of the bursa. Furthermore, the coraco-acromial ligament partially intervenes" —evidently between the head of the humerus and the acromion! It is difficult to see why the shoulder joint ". . . is anatomically not likely to show the usual changes associated with arthritis" (p. 356) and that "from our understanding of accepted principles of pathology, such actual destruction by friction is well nigh impossible" (p. 357).

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[22] Codman, Ernest A., and Akerson, Irving B.: The Pathology Associated with Rupture of the Supraspinatus Tendon, Ann. Surg. **93**:348-359, 1931.

These authors further stated that "a feeble effort at repair" may result in ". . . the formation of a falciform edge (in the vertical plane) of fibrosynovial tissue which smooths the edge of the rupture around the whole circumference [pp. 354-355] . . . The rents in the other tendons extend laterally from that in the supraspinatus, even to the extent of evulsion of all of the tendons of the short rotators" [p. 356]. Certainly, no one will deny that all the tendons of the short rotator muscles may be evulsed, but surely not without a history of serious trauma and recourse on the part of the patient to immediate treatment, thus throwing the condition wholly outside of the category of those that I considered and attributed to attrition.

It is noteworthy that Codman, who has given so much and such long attention to these matters in living subjects, said in 1934[5] (p. 84) that although he enjoyed the cooperation of friends he never saw a fresh rupture of the supraspinatus tendon on the operating table or at autopsy and never operated on a *young* man and "demonstrated" the presence of a ruptured tendon. The average age in his series of patients with assumed complete rupture of the supraspinatus tendon was 55, and of partial rupture, 49 years! The fact that none of the cases of so-called rupture mentioned by Codman occurred before the age of 50 and that none came to his attention for weeks or months after the presumed rupture surely is of great significance and cannot be explained by Codman's belief that partial acute ruptures are painless.

Codman regarded all communications between the subdeltoid bursa and the joint cavity as "pathologic" and suggested arthritis, periarthritis, bursitis, chronic inflammation and possibly overuse as causes for rupture of the tendon of the supraspinatus muscle. Yet he expressed the belief (p. 97) that rupture of this tendon is usually caused by sudden elevation of the arm, not under a load but merely in order to maintain body balance when in a drunken state! This idea was emphasized further on page 134, where it is said that "adequate injury—usually a fall" is responsible for the rupture.

Although bony excrescences were present in the case shown in his figure 3, plate 4, Codman stated that he found no evidences of pathologic changes, but on page 108 it is stated that he now believes that trauma and arthritis play alternating parts and (p. 109) that "some toxic disturbance" may render the "joint tissues and the adjacent tendons sub-normal, and even partially necrotic, so that slight traumata which would not affect a normal tendon, easily tore their fibers." On page 112 of this same work it is said that:

> . . . it is fair to postulate that most of the operative cases had some degree of "arthritic" degeneration in their musculo-tendinous cuffs before their accidents (p. 112). . . . When I first began my work on "Stiff and Painful Shoulders," the usual diagnosis assigned to such cases was "periarthritis." Following my articles drawing attention to the anatomic characteristics of the bursa and the importance of its recognition, the term "subdeltoid bursitis" replaced that of "periarthritis," and since my second paper, the adjective "subacromial" has largely replaced that of "subdeltoid" (p. 119); . . . we might say with much truth that there is no such condition as a chronic arthritis *per se* of the shoulder, for, owing to the structure of the joint, it would always be a periarthritis; . . . I contend that the defects in this cuff so frequently found at autopsy were originally largely traumatic, although unhealthy tendon may have suffered the trauma (pp. 117-118), . . . tendinitis both of the calcified and uncalcified forms precedes the peaks of incidence of the ruptures, partial and complete, by about five to ten years (p. 138).

According to Codman (p. 122), complete rupture of the supraspinatus tendon causes a chronic bursitis, and inflammation of the tendon probably remains painless until a subacromial bursa becomes involved. He further expressed the belief (p. 121) that hyperabduction of an arm for a period of one to two hours may cause a bursitis which may last for half a year; that [23] the strain on the subdeltoid bursa in operations on the breast may cause bursitis; that this is the rule rather than the exception, and that "brachial neuritis" usually is a bursitis.

Excellent evidence against the assumption that the lesions I have considered are pathologic in origin is afforded by the cartilaginous changes observed by Glauning [24] in the knee joints of horses. Except in two respects, these were wholly comparable to those found in the human being, and Glauning stated that none of the animals had been lame and that the changes observed were not due to inflammatory conditions. This is in accord with the findings in worn human tissues from the dissecting room which likewise revealed no evidences of disease.

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[23] Codman, Ernest A.: Rupture of the Supraspinatus Tendon, Surg., Gynec. & Obst. **52**:579-586, 1931.

[24] Glauning, Werner: Altersveränderungen im Kniegelenk des Pferdes, Inaug. Dissert., Habbel, Regensburg, 1936.

INFLUENCE OF LAPAROTOMY ON THE GASTRIC MOTOR MECHANISM OF MAN

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Disturbances in the motility of the stomach are frequently encountered after laparotomy. These may become of serious import if the underlying morbid process is not corrected. In this respect an understanding of the perverted physiologic activities of the human stomach is of peculiar importance, for without it therapy is uncertain and may prove to be unsuccessful.

To investigate certain of the problems which arise concerning pathologic gastric physiologic activity, preliminary observations were made on the influence of the extrinsic innervation on the motility of the human stomach. Unusual opportunities were available for studying the effect of resection of the splanchnic and of the vagus nerves on the gastric motor function. The surgical indications, the apparatus used and an analysis of the results obtained have already been reported.[1] The results of these fundamental observations led us to make an analysis of certain abnormal gastric manifestations so frequently encountered after laparotomy. The purpose of this paper is to report the results of this investigation.

METHOD OF INVESTIGATION

Gastric motility was studied in seven patients. Two presented cholecystitis associated with cholelithiasis for which cholecystectomy was eventually performed with the patients under nitrous oxide-ether anesthesia. Five were operated on for inguinal hernia. In this group spinal anesthesia was used for four patients and nitrous oxide-ether anesthesia for the fifth.

In the first group both patients presented the findings characteristic of disease of the biliary tract. Roentgenographic studies revealed in one patient numerous

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[1] Barron, Louis E.; Curtis, George M., and Haverfield, William T.: The Effect of Bilateral Resection of the Splanchnic Nerves on Gastric Motility in Man, Arch. Surg. **32**:577 (April) 1936. Barron, Louis E.; Curtis, George M.; Haverfield, W. T., and Lauer, B.: Effect of Vagotomy on the Gastric Motor Mechanism of Man, ibid. **34**:1132 (June) 1937.

opaque shadows suggestive of facetted gallstones. In the other there was nonvisualization of the gallbladder after the intravenous administration of the dye. The diagnosis of cholecystitis associated with cholelithiasis was confirmed for both patients at operation.

Tracings of the gastric motility were made during prolonged preoperative control periods. Observations were resumed as soon as postoperative nausea and vomiting subsided. This was approximately four days after cholecystectomy.

In the second group one patient presented bilateral indirect inguinal hernia. Herniorrhaphy was performed in two stages. Tracings of the gastric motility were made during the preoperative control period, during the first operation and throughout an intervening ten day period and were resumed subsequent to the second operation. It thus became possible to compare the results of two separate but similar operations on the same patient. Since spinal anesthesia was employed for four patients, tracings of the gastric motility were possible during the actual hernial repair as well as immediately after the surgical procedure. Daily observations were continued on all patients until they were discharged from the hospital.

Gastric motility was investigated by the balloon and kymograph method. The specific details of this procedure and the manner of ascertaining the position of the balloon in the stomach, as well as the method of analyzing the results, have been described.[1] Observations were made in the morning about fourteen hours after the evening meal. The usual duration of each continuous observation was about five hours. Tracings of the gastric motility were also made on the morning of operation to note any disturbances in motility possibly associated with emotional changes resulting from anticipation of the surgical procedure.

The specific criteria for the evaluation of gastric motility were essentially the same as those described in the earlier reports.[1] The data obtained from each patient were similarly arranged in tabulated form to facilitate accurate comparative study. Those appearing in this paper are representative. In a few instances a signal magnet and electric key were incorporated into the system. The patients were instructed to indicate any abdominal discomfort by pressing the key, which in turn produced an informative mark on the tracing, thereby making it possible to note any correlation between the abdominal symptoms and the results appearing on the kymographic record.

RESULTS

When the results of this investigation were surveyed in their entirety, it was evident that variation was present. It would seem that the specific disease, its duration and the eventual surgical management were responsible, at least in part, for this. As a consequence, the results are presented with reference to the primary disease and its subsequent therapy.

Cholecystitis with Cholelithiasis.—During the preoperative control period the duration of periods of motility was somewhat increased (table 1). In many instances they persisted for more than one hundred minutes (fig. 1). Frequently mild epigastric pain was experienced during this prolonged period of gastric activity. By means of the electric key and signal magnet, it appeared that this abdominal discomfort accompanied intense gastric contractions.

TABLE 1.—*Analysis of Experiments on Gastric Motility During the Control Period in a Case of Cholecystitis with Cholelithiasis*

Date of Experiment	Duration of Experiment	Periods of Quiescence		Periods of Activity		Contractions					Comment
		No.	Duration	No.	Duration	Type	No.	Duration	Interval Between	Amplitude	
5/25/35	4 hr.	..	......	1	20 m.	II	23	Max. 55 s.* Min. 20 s.	Max. 3 m. Min. 1 m.	Max. 5 cm. Min. 2.5 cm.	
		1	25 m.	1	77 m.	II	46	Max. 50 s. Min. 20 s.	Max. 3 m. Min. 10 s.	Max. 6 cm. Min. 2.5 cm.	Terminated in tetany
		1	109 m.	..	......	..	..	....	....	....	Fluctuations in tonus
5/26/35	4 hr., 15 m.*	..	......	1	29 m.	II	31	Max. 45 s. Min. 20 s.	Max. 1 m., 30 s. Min. 10 s.	Max. 4 cm. Min. 2 cm.	Terminated in tetany
		1	10 m.	1	120 m.	II	77	Max. 1 m. Min. 30 s.	Max. 4 m., 15 s. Min. 20 s.	Max. 4 cm. Min. 1.5 cm.	
		1	14 m.	1	70 m.	II	53	Max. 1 m. Min. 35 s.	Max. 2 m. Min. 40 s.	Max. 5 cm. Min. 2.5 cm.	
		1	14 m.	1	22 m.	II	17	Max. 45 s. Min. 20 s.	Max. 1 m., 20 s. Min. 55 s.	Max. 4 cm. Min. 2 cm.	
5/28/35	4 hr., 50 m.	..	......	1	11 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	7 m.	1	282 m.	II	300	Max. 1 m., 5 s. Min. 15 s.	Max. 1 m., 20 s. Min. 15 s.	Max. 3 cm. Min. 1.5 cm.	Symptoms of biliary colic
5/29/35	5 hr.	..	......	1	17 m.	II	19	Max. 55 s. Min. 40 s.	Max. 40 s. Min. 5 s.	Max. 5.5 cm. Min. 2 cm.	
		1	14 m.	1	121 m.	II	58	Max. 55 s. Min. 35 s.	Max. 3 m. Min. 25 s.	Max. 5.5 cm. Min. 2.5 cm.	
		1	24 m.	1	74 m.	II	58	Max. 55 s. Min. 30 s.	Max. 5 m. Min. 10 s.	Max. 5.5 cm. Min. 2.5 cm.	
		1	50 m.								
5/30/35	4 hr.	Continuous gastric motility throughout the observation period; symptoms and signs characteristic of biliary colic									

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* In this and the following tables m. indicates minutes; s., seconds; Max., maximum, and Min., minimum.

An increase in the usual amplitude of contractions was also observed. Frequently this was as much as from 8 to 10 cm. (table 1). The interval between contractions was about two minutes, and the usual duration of each contraction was about one minute.

The duration of the period of gastric quiescence was variable and was attended by no epigastric distress. During such periods it was possible to observe low grade fluctuations in gastric tonus. Respiratory excursions were evident on the kymographic tracings. With the resumption of intense gastric motility there frequently ensued a recurrence of epigastric distress simultaneous with the severe contractions. In a few instances tracings were obtained during attacks of abdominal pain, which from the standpoint of intensity and radiation was characteristic of biliary colic. The gastric motility under such circumstances was continuous throughout observation periods of from four to five hours (fig. 2), during which severe contractions were occasionally noted.

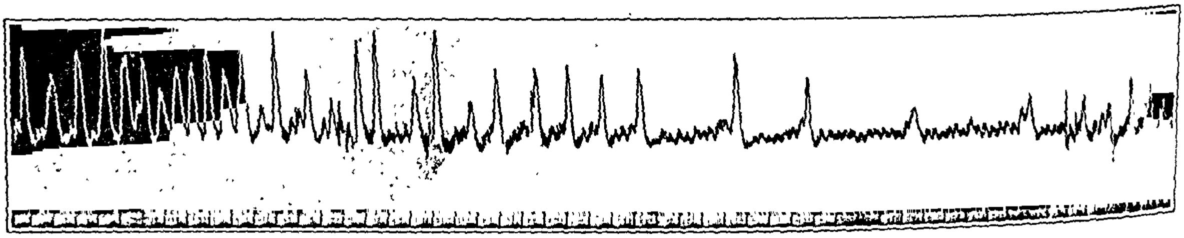

Fig. 1.—Tracing made on May 26, 1935, showing the persistence of gastric motility for one hundred and twenty minutes in a patient with untreated cholelithiasis.

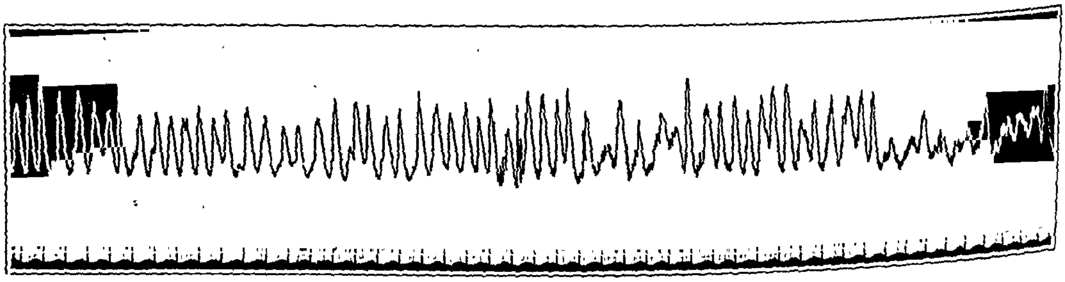

Fig. 2.—Tracing made on May 28, 1935, showing continuous gastric motility during biliary colic. The duration of this period was two hundred and eighty-two minutes.

The use of general anesthesia prohibited the study of gastric motility during cholecystectomy. However, on the morning of the fourth postoperative day studies were resumed and serial observations continued. These revealed definite hypermotility, more pronounced than that of the control period and persisting throughout an observation period of approximately three hours (fig. 3). The amplitude of the contractions was definitely increased (table 2).

Epigastric distress appeared to parallel these periods of hypermotility during which severe contractions were evident. At the termination of the observations the patients complained of abdominal discomfort, which was invariably interpreted as "gas pains" (fig. 3). Subjectively these sensations persisted for about a week after cholecystectomy. However, the hypermotility persisted for a longer period (table 2). As a late manifestation, the patients complained of intense hunger (fig. 4). The entire duration of the period of postoperative hypermotility was approximately three weeks. Subsequently the motility returned to normal.

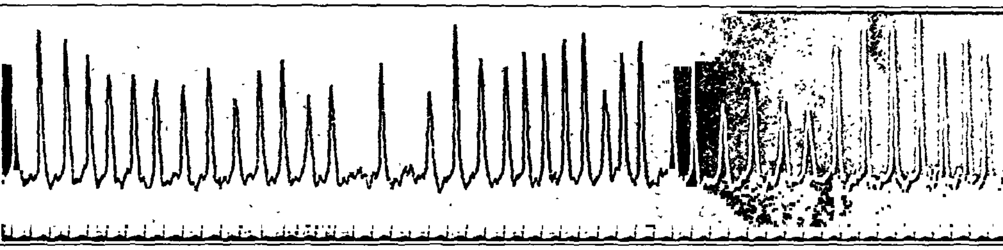

Fig. 3.—Tracing made on June 4, 1935, four days after cholecystectomy, showing intense gastric motility persisting for one hundred and eighty-two minutes. At the termination of this period, the patient complained of "gas pains."

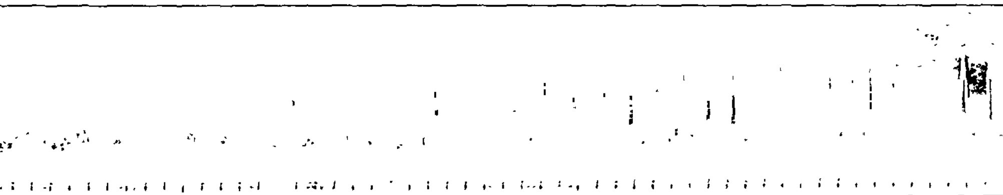

Fig. 4.—Tracing made on June 12, 1935, twelve days after cholecystectomy, showing intense gastric motility associated with hunger. The duration of this period was one hundred and forty-four minutes.

Herniorrhaphy.—Gastric motility was studied on five patients with inguinal hernia. Herniorrhaphy was eventually performed after adequate control studies (table 3). Tracings were also obtained on the morning of operation. On four patients records were made during the operative procedure, which was conducted with low spinal anesthesia. Studies were then resumed immediately after the repair. The duration of these periods of observation varied, but on the whole they were approximately four hours. Daily observations were then made in the morning until the patient was discharged from the hospital. The results were similar in all five patients.

TABLE 2.—*Analysis of Experiments on Gastric Motility After Cholecystectomy*

Date of Experiment	Duration of Experiment	Periods of Quiescence		Periods of Activity		Contractions					Comment
		No.	Duration	No.	Duration	Type	No.	Duration	Interval Between	Amplitude	
6/ 4/35	4 hr.	..	......	1	182 m.	II	132	Max. 1 m. Min. 25 s.	Max. 3 m., 10 s. Min. 55 s.	Max. 6 cm. Min. 2.5 cm.	
		1	13 m.	1	45 m.	II	27	Max. 50 s. Min. 20 s.	Max. 3 m., 20 s. Min. 55 s.	Max. 6 cm. Min. 3.5 cm.	Complained of gas pains
6/ 5/35	4 hr., 35 m.	..	......	1	104 m.	II	60	Max. 55 s. Min. 25 s.	Max. 5 m., 40 s. Min. 10 s.	Max. 6.5 cm. Min. 2 cm.	
		1	25 m.	1	75 m.	II	38	Max. 1 m. Min. 30 s.	Max. 4 m. Min. 35 s.	Max. 6.5 cm. Min. 3 cm.	
		1	16 m.	1	55 m.	II	20	Max. 50 s. Min. 20 s.	Max. 4 m., 15 s. Min. 1 m., 30 s.	Max. 6 cm. Min. 2.5 cm.	Complained of gas pains
6/ 6/35	4 hr., 50 m.	..	......	1	44 m.	II	35	Max. 1 m. Min. 15 s.	Max. 5 m., 20 s. Min. 20 s.	Max. 4.5 cm. Min. 2.5 cm.	
		1	22 m.	1	169 m.	II	121	Max. 55 s. Min. 35 s.	Max. 6 m. Min. 5 s.	Max. 6 cm. Min. 2.5 cm.	
		1	10 m.	1	45 m.	II	38	Max. 1 m., 20 s. Min. 30 s.	Max. 2 m., 15 s. Min. 40 s.	Max. 6 cm. Min. 2 cm.	Complained of gas pains
6/ 8/35	4 hr., 15 m.	..	......	1	50 m.	II	20	Max. 1 m. Min. 30 s.	Max. 5 m., 10 s. Min. 1 m.	Max. 5 cm. Min. 1.5 cm.	
		1	54 m.	1	20 m.	II	10	Max. 1 m. Min. 40 s.	Max. 3 m. Min. 35 s.	Max. 4.5 cm. Min. 1.5 cm.	
		1 1	12 m. 103 m.	1	16 m.	II	10	Max. 50 s. Min. 30 s.	Max. 2 m., 35 s. Min. 25 s.	Max. 4.5 cm. Min. 2 cm.	
6/10/35	2 hr., 30 m.	Continuous motility throughout observation period; patient complained of nausea and epigastric distress									
6/12/35	4 hr.	..	......	1	19 m.	II	23	Max. 1 m. Min. 20 s.	Max. 1 m. Min. 10 s.	Max. 4.5 cm. Min. 2.5 cm.	
		1	9 m.	1	144 m.	II	114	Max. 1 m. Min. 40 s.	Max. 2 m., 30 s. Min. 40 s.	Max. 5 cm. Min. 2.5 cm.	

		1	9 m.	1	59 m.	II	36	Max. 45 s. Min. 20 s.	Max. 4 m. Min. 35 s.	Max. 4.5 cm. Min. 1.5 cm.	Complained of hunger
6/13/35	3 hr.	..	......	1	13 m.	II	16	Max. 1 m. Min. 30 s.	Max. 1 m. Min. 5 s.	Max. 4 cm. Min. 2 cm.	
		1	9 m.	1	158 m.	II	92	Max. 1 m. Min. 45 s.	Max. 5 m. Min. 20 s.	Max. 5 cm. Min. 1.5 cm.	
6/15/35	3 hr.	..	......	1	7 m.	III	Inestimable	Inestimable	Inestimable	....	Gastric tetany
		1	5 m.	1	28 m.	II	25	Max. 50 s. Min. 10 s.	Max. 1 m. Min. 15 s.	Max. 4.5 cm. Min. 2 cm.	Terminated in tetany
		1	7 m.	1	133 m.	II	136	Max. 1 m. Min. 25 s.	Max. 1 m., 50 s. Min. 20 s.	Max. 5 cm. Min. 1.5 cm.	Complained of hunger
6/17/35	3 hr., 25 m.	..	......	1	9 m.	II	10	Max. 25 s. Min. 15 s.	Max. 20 s. Min. 5 s.	Max. 5 cm. Min. 2 cm.	
		1	5 m.	1	39 m.	II	12	Max. 50 s. Min. 20 s.	Max. 1 m. Min. 5 s.	Max. 4 cm. Min. 1.5 cm.	
		1	5 m.	1	147 m.	II	151	Max. 1 m. Min. 25 s.	Max. 1 m., 10 s. Min. 5 s.	Max. 4 cm. Min. 1.5 cm.	
6/18/35	3 hr., 5 m.	..	......	1	35 m.	II	22	Max. 35 s. Min. 25 s.	Max. 2 m. Min. 10 s.	Max. 5 cm. Min. 2 cm.	
		1	87 m.	1	63 m.	II	16	Max. 45 s. Min. 30 s.	Max. 3 m. Min. 1 m.	Max. 5.5 cm. Min. 2.5 cm.	Complained of hunger
6/19/35	3 hr.,	1	88 m.	1	92 m.	II	32	Max. 40 s. Min. 10 s.	Max. 10 m. Min. 15 s.	Max. 5 cm. Min. 2 cm.	
6/20/35	4 hr., 35 m.	..	......	1	12 m.	II	0	Max. 1 m., 25 s. Min. 20 s.	Max. 1 m. Min. 10 s.	Max. 5 cm. Min. 3.5 cm.	
		1	99 m.	1	35 m.	II	23	Max. 45 s. Min. 20 s.	Max. 2 m., 40 s. Min. 20 s.	Max. 2.5 cm. Min. 2 cm.	
		1	75 m.	1	51 m.	II	17	Max. 45 s. Min. 10 s.	Max. 2 m., 45 s. Min. 1 m., 30 s.	Max. 3 cm. Min. 1.5 cm.	

TABLE 3.—*Analysis of Experiments on Gastric Motility During the Control Period in a Case of Right Indirect Inguinal Hernia*

Date of Experiment	Duration of Experiment	Periods of Quiescence		Periods of Activity		Contractions					Comment
		No.	Duration	No.	Duration	Type	No.	Duration	Interval Between	Amplitude	
11/ 9/35	4 hr., 40 m.	..	......	1	43 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	62 m.	1	36 m.	II	34	Max. 1 m., 5 s. Min. 20 s.	Max. 1 m., 20 s. Min. 5 s.	Max. 4 cm. Min. 2 cm.	
		1	48 m.	1	19 m.	II, III	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 1.5 cm.	
		1	55 m.	1	17 m.	II	12	Max. 1 m. Min. 30 s.	Max. 1 m., 40 s. Min. 20 s.	Max. 3 cm. Min. 2 cm.	
11/11/35	4 hr.	..	......	1	62 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 1.5 cm.	
		1	62 m.	1	35 m.	II	35	Max. 1 m. Min. 15 s.	Max. 2 m. Min. 10 s.	Max. 4.5 cm. Min. 2 cm.	
		1	47 m.	1	22 m.	II	27	Max. 30 s. Min. 5 s.	Max. 1 m. Min. 5 s.	Max. 4 cm. Min. 1.5 cm.	Terminated in tetany
		1	12 m.								
11/12/35	4 hr., 30 m.	..	......	1	25 m.	II	18	Max. 30 s. Min. 10 s.	Max. 2 m. Min. 10 s.	Max. 4.5 cm. Min. 2 cm.	
		1	213 m.	1	35 m.	II	31	Max. 50 s. Min. 5 s.	Max. 1 m. Min. 5 s.	Max. 5 cm. Min. 2 cm.	
11/13/35	5 hr., 45 m.	..	......	1	23 m.	I	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 2 cm.	
		1	59 m.	A few low grade contractions noted							
		1	51 m.	1	38 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 1.5 cm.	
		1	41 m.	1	54 m.	II	40	Max. 1 m. Min. 5 s.	Max. 2 m., 30 s. Min. 5 s.	Max. 5 cm. Min. 2 cm.	
		1	79 m.	..	......	..	..	....	....	....	Fluctuations in tonus

11/14/35	5 hr., 45 m.	..	......	1	48 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 1.5 cm.	
		1	27 m.	1	20 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 2.5 cm. Min. 1.5 cm.	
		1	99 m.	1	41 m.	II	33	Max. 1 m., 30 s. Min. 5 s.	Max. 2 m. Min. 5 s.	Max. 4 cm. Min. 2 cm.	
		1	104 m.	Few contractions during this period							
11/15/35	5 hr., 30 m.	..	......	1	41 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 4.5 cm. Min. 2 cm.	
		1	41 m.	1	34 m.	II	33	Max. 1 m. Min. 5 s.	Max. 2 m., 30 s. Min. 5 s.	Max. 4 cm. Min. 1.5 cm.	Terminated in tetany
		1	70 m.	1	20 m.	II	25	Max. 50 s. Min. 5 s.	Max. 1 m. Min. 5 s.	Max. 4 cm. Min. 2 cm.	
		1	59 m.	1	32 m.	II	30	Max. 55 s. Min. 5 s.	Max. 1 m., 15 s. Min. 5 s.	Max. 5 cm. Min. 2.5 cm.	
		1	21 m.								
11/17/35	4 hr., 35 m.	..	......	1	34 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1.5 cm.	
		1	76 m.	1	35 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1.5 cm.	
		1	54 m.	1	23 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 2 cm.	
		1	55 m.								
11/18/35	5 hr., 50 m.	..	......	1	10 m.	II, III	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1.5 cm.	Terminated in tetany
		1	40 m.	1	18 m.	II, III	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1 cm.	Terminated in tetany
		1	61 m.	1	40 m.	II, III	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 1 cm.	
		1	23 m	1	30 m.	II, III	Inestimable	Inestimable	Inestimable	Max. 4 cm. Min. 1.5 cm.	Terminated in tetany
		1	70 m.	1	28 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 4.5 cm. Min. 2 cm.	
11/19/35	3 hr., 15 m.	..	.....	1	20 m.	II, III	Inestimable	*Inestimable*	Inestimable	Max. 4.5 cm. Min.2.5 cm.	*Epigastric distress*
		1	105 m.	1	21 m.	II, III	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 2 cm.	Terminated in tetany
		1	13 m.	Herniorrhaphy on right side at 10:15 a. m.; gastric inhibition throughout operation							

TABLE 4.—*Analysis of Experiments on Gastric Motility During and After Herniorrhaphy on Right Side*

Date of Experiment	Duration of Experiment	Periods of Quiescence		Periods of Activity		Contractions					Comment
		No.	Duration	No.	Duration	Type	No.	Duration	Interval Between	Amplitude	
11/19/35	3 hr., 30 m.	Gastric inhibition throughout observation period; tracing made immediately after herniorrhaphy									
11/20/35	3 hr., 5 m.	Continuous low grade motility; occasional contraction of high amplitude									
11/21/35	3 hr., 15 m.	Continuous low grade motility throughout observation period									
11/22/35	5 hr., 8 m.	..	......	1	13 m.	II	11	Max. 45 s. Min. 10 s.	Max. 1 m. Min. 20 s.	Max. 3.5 cm. Min. 1.5 cm.	
		1	17 m.	1	18 m.	II	19	Max. 50 s. Min. 5 s.	Max. 1 m., 10 s. Min. 5 s.	Max. 3 cm. Min. 1 cm.	Terminated in tetany
		1	8 m.	1	45 m.	II	43	Max. 1 m. Min. 5 s.	Max. 1 m. Min. 5 s.	Max. 4.5 cm. Min. 1.5 cm.	Complained of gas pains
		1	28 m.	1	179 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 4.5 cm. Min. 1.5 cm.	Complained of gas pains
11/23/35	5 hr.	..	......	1	29 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	27 m.	1	23 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1.5 cm.	
		1	71 m.	1	34 m.	I	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 1 cm.	
		1	30 m.	1	86 m.	II	50	Max. 1 m., 10 s. Min. 20 s.	Max. 4 m. Min. 20 s.	Max. 4 cm. Min. 1.5 cm.	Complained of gas pains
11/24/35	4 hr.	..	......	1	28 m.	II	27	Max. 1 m., 30 s. Min. 5 s.	Max. 1 m. Min. 5 s.	Max. 3.5 cm. Min. 1 cm.	Terminated in tetany
		1	56 m.	1	51 m.	II	38	Max. 1 m., 15 s. Min. 5 s.	Max. 2 m. Min. 5 s.	Max. 3.5 cm. Min. 1 cm.	
		1	78 m.	1	27 m.	II	20	Max. 2 m. Min. 5 s.	Max. 2 m., 10 s. Min. 5 s.	Max. 3.5 cm. Min. 1.5 cm.	
11/25/35	5 hr., 15 m.	Continuous motility throughout observation period; patient complained of hunger									
11/26/35	4 hr., 20 m.	Continuous motility throughout observation period; patient complained of hunger									

11/27/35	5 hr.	..	......	1	38 m.	II, III	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 1 cm.	
		1	27 m.	1	26 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 5 cm. Min. 1.5 cm.	
		1	38 m.	1	54 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	59 m.	1	58 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1 cm.	
11/29/35	4 hr.	..	......	1	45 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	63 m.	1	132 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 4.5 cm. Min. 1.5 cm.	Complained of hunger
11/30/35	5 hr., 5 m.	..	......	1	51 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	32 m.	1	34 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	36 m.	1	152 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 3 cm. Min. 1 cm.	
12/ 2/35	5 hr., 25 m.	..	......	1	28 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	48 m.	1	24 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1.5 cm.	
		1	50 m.	1	32 m.	I, II	Inestimable	Inestimable	Inestimable	Max. 3.5 cm. Min. 1.5 cm.	
		1	53 m.	1	41 m.	II	32	Max. 1 m., 10 s. Min. 5 s.	Max. 2 m., 20 s. Min. 5 s.	Max. 3.5 cm. Min. 1.5 cm.	
		1	49 m.								
12/ 3/35	5 hr.	..	......	1	98 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	49 m.	1	95 m.	II	54	Max. 1 m., 50 s. Min. 5 s.	Max. 3 m. Min. 5 s.	Max. 4.5 cm. Min. 2 cm.	Complained of hunger
		1	58 m.								
12/ 4/35	4 hr., 15 m.	..	......	1	41 m.	I	Inestimable	Inestimable	Inestimable	Low grade	
		1	50 m.	1	86 m.	II	55	Max. 2 m. Min. 5 s.	Max. 3 m., 10 s. Min. 5 s.	Max. 4.5 cm. Min. 1.5 cm.	Complained of hunger
		1	78 m								

During the control period some variation was noted (table 3). However, the motility was essentially normal (fig. 5 *A*). Immediately preceding hernial repair there appeared to be a definite increase in the amplitude of the contractions, although in many instances the total duration of the periods of activity was relatively short (fig. 5 *B*). There was evidence of considerable associated emotional disturbance. The patients complained of epigastric distress. There was an apparent relationship between the emotional state and the hypermotility. When spinal anesthesia was induced, the stomach became quiescent. This inhibition of gastric motility, associated with a marked reduction in tonus, continued throughout the operation (fig. 5 *C*).

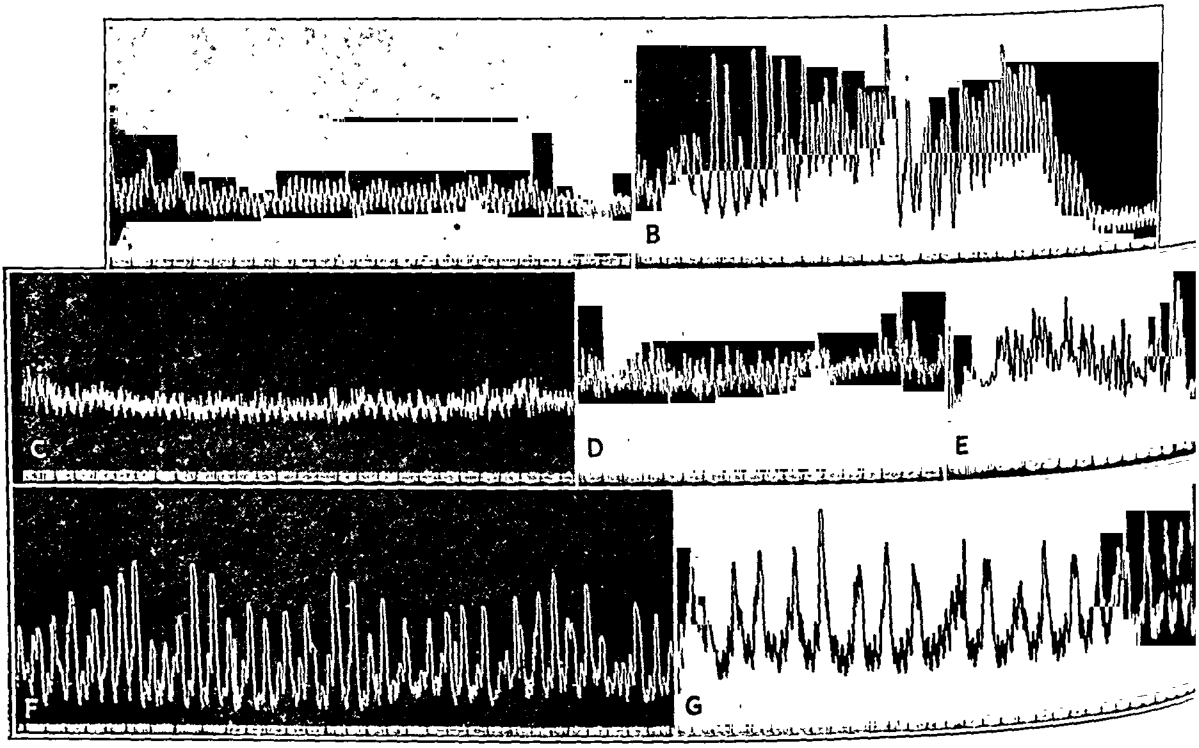

Fig. 5.—Sections *A* to *G* are segments of kymographic tracings obtained on the same patient. *A*, control tracing made on November 12, showing low grade gastric motility in a patient with right indirect inguinal hernia. *B*, tracing made on November 19, about an hour preceding herniorrhaphy. The gastric motility was intense but of short duration. *C*, tracing made on November 19, showing inhibition of the gastric motility during herniorrhaphy. *D*, tracing made on November 19, showing the persistence of inhibition for several hours subsequent to herniorrhaphy. *E*, tracing made on November 20, showing the return of gastric motility twenty-four hours subsequent to herniorrhaphy. *F*, tracing made on November 22, showing continuous motility with intense contractions three days after herniorrhaphy. The duration of this period was one hundred and seventy-nine minutes. At the termination of this observation the patient complained of "gas pains." *G*, tracing made on December 3, two weeks after herniorrhaphy, showing continuous gastric activity associated with hunger.

Inhibition of gastric motility persisted from twenty-four to approximately thirty-six hours subsequent to herniorrhaphy (fig. 5 *D;* table 4). In some instances it continued for seventy-two hours. After this period there was a gradual return of motility (fig. 5 *E*). This manifested itself first by an increase in tonus, superimposed on which were feeble contractions, which grew progressively more intense. About twenty-four to forty-eight hours after the onset of motility, definite hypermotility became evident (fig. 5 *F*). Simultaneous with this the patients complained of epigastric distress, interpreted by them as "gas pains." Hypermotility with intense contractions persisted for about two weeks. However, the sensation of "gas pains" was experienced for approximately one week after operation. Subsequently the patients complained of intense hunger as a late manifestation of hypermotility (fig. 5 *G*). Throughout the postoperative period medication was purposely avoided so that the results of laparotomy would not be obscured. In some patients the hypermotility persisted throughout their entire stay in the hospital. In others the motility approached the preoperative normal prior to discharge.

COMMENT

Preliminary observations on gastric motility revealed some variation among the patients. Therefore, a sufficient number of control studies was made in order to permit of adequate interpretations. The results from each patient were relatively uniform and essentially normal. They were in agreement with the results described by other investigators.[2]

Some evidence of hypermotility during the preoperative period is revealed in the two patients with cholecystitis. Although this was not constant, it was noted with sufficient frequency to be significant. Many tracings exhibited gastric contractions of abnormally great amplitude. When this occurred, the patients frequently complained of abdominal discomfort referable to the epigastrium.

The sensory mechanism which registers abdominal pain in disease of the gallbladder in the conscious patient is exceedingly complex. Theories describing the nervous pathways over which the sensory stimuli travel have been reported in detail elsewhere[3] and therefore are intentionally omitted from this report. The abdominal pain to which we refer was always localized in the epigastrium and was interpreted as a dull, aching, boring distress. It was never associated with nausea or with vomiting. At no time did this discomfort reach sufficient magnitude to indicate termination of the usual period of observation. It did not present the intensity or distribution characteristic of biliary colic.

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[2] Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

[3] Zollinger, Robert: Significance of Pain and Vomiting in Cholelithiasis, J. A. M. A. **105**:1647 (Nov. 23) 1935.

The frequent occurrence of gastric hypermotility with its associated epigastric distress during the period of cholecystitis with cholelithiasis in which treatment was not given would suggest a relationship between disease of the biliary tract and reflex disturbances in gastric motor function. Carlson[2] made observations on the gastric motility of a patient with disease of the gallbladder. He, too, found that epigastric distress ran parallel with the strong contractions of the empty stomach. He also noted that the contractions were stronger than usual for the age of the patient.

This experimental evidence further indicates that in disease of the biliary tract there may be reflex stimulation of the gastric motor mechanism, with ensuing hypermotility of the stomach. Since epigastric distress accompanied the intense gastric contractions, it would seem that there also ensues a reflex stimulation of the sensory nerves of the stomach. However, the evidence is as yet too indefinite to permit the conclusion that gastric hypermotility is the sole cause of the abdominal distress concurrent with disease of the biliary tract. Doubtless other undetermined extragastric factors play a rôle. Nevertheless, the frequency with which hypermotility of the stomach was associated with epigastric distress in these two patients would indicate concomitant disturbances in reflex gastric motor and sensory functions. Carlson[2] noted that the epigastric pain often appeared greater than warranted by the strength of the gastric contractions. He expressed the opinion that infection of the gallbladder might lead to hyperexcitability of the sensory nervous mechanism of the stomach and duodenum, possibly from the spread of bacterial toxins along the branches of the vagus nerves.

Barber[4] and Barber and Stewart[5] also found hypermotility and pylorospasm associated with disease of the gallbladder. They reported that irritation of the gallbladder, duodenum and appendix increased the rate and force of the gastric contractions. Although the exact cause for this is not clear, it was thought to be of vagal origin.

In a few instances we obtained tracings of the gastric motility during attacks of biliary colic. These revealed continuous motility, frequently persisting throughout the period of observation. The amplitude of these contractions was about from 4 to 5 cm.

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[4] Barber, W. Howard: Gas and the Motility of the Surgical Stomach, Ann. Surg. **69**:271, 1919.

[5] Barber, W. Howard, and Stewart, George D.: Further Observations upon Reflex Gastric Hypermotility, Proc. Soc. Exper. Biol. & Med. **17**:155, 1919-1920.

Various manifestations of abnormal gastric motor function have been described as associated with disease of the biliary tract; the most common observations have been pylorospasm and hypermotility of the stomach. McCrea[6] reported that irritation and inflammation of the appendix or of the gallbladder may produce pylorospasm, gastric hypermotility and hyperchlorhydria. He even suggested that these may precede the development of ulcer. Smith and Miller[7] demonstrated that irritation of the mucous membrane of the gallbladder of the anesthetized dog with croton oil was followed by a striking increase in the activity of the stomach. After the administration of atropine, there was a decrease in motility. Held and Roemer[8] showed that disease of the gallbladder was likely to produce spasm of the pylorus with active peristalsis of the proximal portion of the stomach. They cited an instance in which gastrospasm was due to gallstones.

The mechanism responsible for the pylorospasm and gastric hypermotility is not clear. However, Hughson[9] found that trauma to the abdominal viscera was capable of producing reflex contractions of the pylorus and gastric hypermotility. He also observed that as a result of peritoneal irritation there ensued an increase in the emptying time of the stomach which persisted for two weeks to a month. He advanced the hypothesis[9b] that spasm of the pylorus resulting from disease either within or adjacent to the abdominal cavity is solely a result of irritation of the peritoneal surfaces.

Contrary to these findings, Ivy[10] reported that mild stimulation of the biliary tract inhibited gastric motility and that distention of the biliary passages caused pylorospasm and also a marked delay in the evacuation of a barium sulfate meal. He noted that a sudden marked distention produced pylorospasm with nausea and vomiting. This was interpreted as being responsible for the dyspeptic symptoms of disease of the gallbladder. In his opinion the pain of biliary colic is not due to pylorospasm, because the type of referred pain is different, and pain referable to the biliary tract may be obtained in man and in the dog after subtotal gastrectomy.

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[6] McCrea, E. D'Arcy: The Nerves of the Stomach and Their Relation to Surgery, Brit. J. Surg. **13**:621, 1926.

[7] Smith, Fred M., and Miller, G. H.: A Study of the Reflex Influence of the Colon, Appendix and Gall Bladder on the Stomach, Am. J. Physiol. **90**:518, 1929.

[8] Held, I. W., and Roemer, J.: Gastrospasm: A Clinical and Roentgenological Study, Am. J. M. Sc. **164**:188, 1922.

[9] Hughson, Walter: (*a*) The Effect of Vagus Neurotomy on the Pyloric Sphincter: An Experimental Study, J. A. M. A. **88**:1072 (April 2) 1927; (*b*) Reflex Spasm of the Pylorus and Its Relation to Diseases of the Digestive Organs, Arch. Surg. **11**:136 (July) 1925.

[10] Ivy, A. C.: (*a*) The Applied Physiology of the Gastro-Intestinal Innervation, Am. J. Digest. Dis. & Nutrition **1**:845, 1935; (*b*) Physiology of the Gall Bladder, Physiol. Rev. **14**:1, 1934.

The reports of various investigators thus indicate that pylorospasm is frequently associated with disease of the gallbladder. Whether this is due to local mechanism or to reflex action by way of the splanchnic or vagus nerves is not clear. However, it is well established that motor and inhibitory fibers enter the pylorus through the vagus and splanchnic nerves and that stimulation of either may result in pylorospasm.

Carlson and Litt [11] found that motor disturbances of the pylorus may be induced not only by local pathologic conditions in the stomach and duodenum or by abnormal states of the central nervous system but by excessive irritation of most, if not all, sensory nerves, particularly those of the abdominal viscera. Clinically, it is known that abnormalities in the gastric motor mechanism may occur during periods of emotional disturbances. Many investigators [12] have reported that under such circumstances gastric motility is inhibited. Similar results have been reported by Ivy,[10a] Carlson [2] and others.[13] On the other hand, there are several investigators who maintain that hypermotility is the most common observation.[14] There is consequently a lack of uniformity in the composite results reported in the literature.

Since it was possible to study gastric motility in patients who were experiencing the emotional disturbance which usually precedes a major operation, kymographic tracings were made for periods of about three hours preceding herniorrhaphy and were continued until the patients were taken to the operating room. It was our experience that gastric hypermotility was the most common observation under these circumstances. In many instances the contractions were severe, although the duration of the periods of gastric activity was not unusually prolonged. By means of the electric key and the signal magnet it was possible to observe that epigastric distress occurred during periods of intense motility.

We cannot conclude from our own findings or from the reports of other investigators that either hypermotility or inhibition necessarily occurs during emotional states. It is possible that either may appear, depending on the preexisting tonus of the stomach and the type of emotional distress manifested. This problem is complex and doubtless is influenced by a multiplicity of factors, which are neither constant nor uniform throughout the studies made by various investigators—hence the discrepancies.

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[11] Carlson, A. J., and Litt, S.: Studies on the Visceral Nervous System: On the Reflex Control of the Pylorus, Arch. Int. Med. **33**:281 (March) 1924.

[12] Cannon, W. B.: The Movements of the Stomach Studied by Means of the Röntgen Rays, Am. J. Physiol. **1**:359, 1898. Todd, T. Wingate: Behavior Patterns of the Alimentary Tract, Baltimore, Williams & Wilkins Company, 1930.

[13] Luckhardt, Arno B.: The Effect of Dreaming on the Gastric Hunger Contractions, Am. J. Physiol. **39**:330, 1915-1916.

[14] Barber.[4] Hughson.[9b]

Although it was our experience to observe hypermotility during the emotional changes preceding operation, it is impossible to conclude that it will uniformly occur until emotions are more clearly defined and more accurately investigated.

Motor inhibition of the gastro-intestinal tract is frequently encountered during abdominal laparotomy. This phenomenon was described by Pal as early as 1890.[15] Since then it has been reported by many investigators. Bayliss and Starling[16] found that when the abdomen of a dog was opened in a warm bath of saline solution the intestines were collapsed and motionless. Section of the splanchnic nerves or even radical destruction of the spinal cord was necessary to institute intestinal motility. Similarly, Meltzer and Auer[17] reported that merely cutting the skin in the linea alba of a rabbit was sufficient to abolish peristalsis of the cecum. Auer[18] observed that opening the abdominal cavity of the rabbit caused cessation of gastric movements. Our studies on the human stomach are in agreement with these experimental observations.

We observed inhibition of the gastric motility during herniorrhaphy. This persisted for a varying period, of from twenty-four to approximately seventy-two hours, postoperatively. It would seem that this temporary gastric paresis was due to reflex stimulation of the splanchnic nerves and due to a mechanism similar to that described by Markowitz and Campbell[19] and Ochsner, Gage and Cutting[20] for the production of physiologic ileus. Our tracings show that the motility eventually returned and that hypermotility subsequently ensued.

During this postoperative period of temporary inhibition of gastric motility or physiologic paralysis of the stomach, gastric distention was most evident. It is possible that this distention, if sufficiently extensive,

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15. Pal, J.: Ueber den Einfluss des Bauchschnittes auf die Darmbewegung, Centralbl. f. Physiol. **4**:338, 1890.

16. Bayliss, W. M., and Starling, E. H.: The Movements and Innervation of the Small Intestine, J. Physiol. **24**:99, 1899.

17. Meltzer, S. J., and Auer, J.: Peristaltic Movements of the Rabbit's Cecum and Their Inhibition, Proc. Soc. Exper. Biol. & Med. **4**:37, 1907.

18. Auer, John: Gastric Peristalsis Under Normal and Certain Experimental Conditions, Proc. Soc. Exper. Biol. & Med. **4**:8, 1907.

19. Markowitz, J., and Campbell, Walter R.: The Relief of Experimental Ileus by Spinal Anesthesia, Am. J. Physiol. **81**:101, 1927.

20. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: Treatment of Ileus by Splanchnic Anesthesia, J. A. M. A. **90**:1847 (June 9) 1928.

acts as a stimulus to the gastric motor mechanism so that hypermotility follows. In 1904 May[21] reported that hypermotility occurred when the dog's excised stomach was inflated with air. Lim, Ivy and McCarthy[22] made similar observations. They found that when overdistention occurred there ensued a decrease in motility and in tone. It would seem from our observations that the distention occurring during this physiologic adynamic period increased until it reached the maximal threshold level peculiar to each patient. The ensuing hypermotility was then probably the result of mechanical stimulation to the gastric motor mechanism in a manner similar to that previously reported. This postoperative hypermotility persisted for from ten days to two weeks. Occasionally it was seen throughout the entire period of postoperative convalescence. In other instances it returned to normal prior to the patient's discharge from the hospital.

It is probable that reflex stimulation of the gastric sensory mechanism occurs simultaneously with the hypermotility of the stomach. The most common subjective sensation experienced by the patients during the early postoperative period of increased gastric activity was a form of epigastric distress interpreted by them as gas pains. These were intermittent and coincided with the severe contractions. Subsequently the patients complained of intense hunger as a late manifestation of increased gastric activity.

Although the early postoperative epigastric distress was interpreted as gas pains and although this occurred during a period of intense gastric activity, we do not think that the hypermotility alone is responsible for this sensation. Obviously there are other factors intimately involved in this problem. Nevertheless, there was sufficient evidence to indicate that in the genesis of postoperative epigastric distress the gastric motor mechanism assumed an important rôle. We would think that inhibition of the gastric motility followed by the hypermotility has certain clinical implications which are significant in understanding the nature of early postoperative disturbances.

The spinal anesthesia which was used during the repair of the hernias did not extend beyond the operative field. The work of other investigators[23] reveals that hypermotility of the gastro-intestinal tract ensues only if the spinal anesthesia produces paralysis of the splanchnic nerves. We observed no evidence that this occurred during our studies.

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[21] May, W. Page: The Innervation of the Sphincters and Musculature of the Stomach, J. Physiol. **31**:260, 1904.

[22] Lim, Robert K. S.; Ivy, A. C., and McCarthy, J. E.: Contributions to the Physiology of Gastric Secretion: I. Gastric Secretion by Local (Mechanical and Chemical) Stimulation, Quart. J. Exper. Physiol. **15**:13, 1925.

[23] Markowitz and Campbell.[10] Ochsner, Gage and Cutting.[20]

Although we cannot outline with certainty the physiologic mechanism responsible for the production of this inhibition during laparotomy and for a varying period subsequently, we do not think that spinal anesthesia per se is the cause. The work of Markowitz and Campbell [19] and Ochsner, Gage and Cutting [20] would lead us to believe that spinal anesthesia is responsible for hypermotility as a result of paralysis of the splanchnic nerves. This hypermotility occurred after an extremely short latent period.

The hypermotility evident on our tracings appeared from one to three days subsequent to operation. Therefore, it is our belief that the mechanism which is responsible for the inhibition of gastric motility which we observed during operation and for a varying period subsequently is similar to the mechanism which is responsible for the inhibition of the intestinal motility during laparotomy, a phenomenon already described.[10] The hypermotility which followed might possibly be due to stimulation of the gastric motor mechanism by the mechanical distention of the stomach occurring during the period of inhibition.

CONCLUSIONS

Gastric motility was studied by the balloon and kymograph method on seven patients on whom laparotomy was performed. The results of this investigation revealed the following facts:

1. There was a tendency toward hypermotility of the stomach in patients with untreated cholecystitis associated with cholelithiasis.
2. Continuous gastric motility was associated with occasional severe contractions during biliary colic.
3. Increased gastric hypermotility persisted for from two to three weeks after cholecystectomy. During the first week of this increased motility the patients experienced epigastric distress interpreted by them as gas pain; subsequently they complained of intense hunger as a late manifestation of hypermotility.
4. Normal gastric motility was present in five patients with inguinal hernia until immediately preceding hernial repair, at which time short but intense periods of gastric activity, associated with emotional disturbance, were observed.
5. Inhibition of gastric motility persisted throughout herniorrhaphy and for from twenty-four to seventy-two hours subsequently.
6. Gastric hypermotility subsequent to inhibition persisted for from two to three weeks, during which the subjective sensations were similar to those described after cholecystectomy.

CARCINOMA OF THE FEMALE BREAST

WITH SPECIAL CONSIDERATION OF PREOPERATIVE IRRADIATION: A PRELIMINARY REPORT

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In the recent surgical literature there are seven articles to which I should like to call special attention.[1] Six of these deal with preoperative irradiation in the treatment of carcinoma of the breast. The seventh is concerned chiefly with the statistical study of cancers of the breast treated by surgical measures alone and by surgical measures and postoperative irradiation. From one of these articles, namely, that of Adair and Stewart, I have taken the following data on eighty-one cases of operable carcinoma of the breast in which preoperative irradiation was followed by a radical Halstead operation.

Radium element pack	39 cases
No residual cancer	11 cases (28%)
Roentgen therapy, 200 kilovolts	42 cases
No residual cancer	7 cases (16%)

In each of these cases biopsy was performed preliminary to irradiation.

In the *Nova Scotia Medical Bulletin* of June 1935 Bloodgood gave his conclusions in favor of irradiation preliminary to operation for carcinoma of the breast.

Bloodgood and Stewart, in a brief paper in the *Southern Medical Journal* for July 1936, made further remarks on the preoperative irradiation of cancer of the breast and reported a case which I shall refer to again in this article.

From the clinic of the late Dr. Joseph C. Bloodgood and his associates.

[1] Bloodgood, Joseph Colt: The Problem of the Breast Tumor, Nova Scotia M. Bull. **14**:307 (June) 1935. Cohn, L. Clarence: Benign Breast Lesions, with Special Consideration of Border-Line Tumors: Cancer of the Breast and the Newer Conception of Preoperative Irradiation, West Virginia M. J. **31**:1 (Jan.) 1936. Adair, Frank E., and Stewart, Fred W.: The Value of Preoperative Irradiation in Breast Cancer, Ann. Surg. **102**:254 (Aug.) 1935. Hutchinson, R. G.: The Value of Radiation Therapy in the Treatment of Carcinoma of the Breast, Surg., Gynec. & Obst. **62**:653 (April) 1936. Nicolson, W. P., and Berman, M. D.: Carcinoma of the Breast: A Study of Five Year End-Results, Ann. Surg. **103**:683 (May) 1936. Graham, Allen: Cancer of the Breast, with Particular Reference to Irradiation as a Factor in End-Results, Pennsylvania M. J. **39**:561 (May) 1936. Bloodgood, Joseph Colt, and Stewart, G. A.: Preoperative Irradiation of Breast Tumors, South. M. J. **29**:651 (July) 1936.

My first experience with the preoperative irradiation of operable cancer of the breast was in 1927, almost ten years ago, and was what might be described as an accident. This concerned a married woman aged 42, whose youngest child was 9 years of age.

I examined the patient with Dr. Bloodgood on March 28, 1927, and we found a gland the size of a 5 cent piece in the base of the right axilla, with a smaller definite nodule in the periphery of the right breast just adjoining the gland. She had felt the lump only four days. Although the roentgenogram of the chest was normal, we decided to use irradiation for the first treatment because of the possibility of lymphosarcoma. When I examined her on May 2, more than four weeks later, and two weeks after roentgen therapy (200 kilovolts), the lump had decreased in size two-thirds and was smaller than a 10 cent piece. As the nodule did not disappear, I decided to do a complete axillary dissection. I made the usual axillary incision as in the complete operation for cancer of the breast, divided the pectoralis major and minor muscles, exposed the axillary vein and dissected the axilla from above downward. On introducing the finger beneath the palpable tumor, finding that the tumor felt like cancer and that it would be necessary to remove a considerable portion of the breast to give the tumor the proper margin, I decided on the usual complete operation for cancer of the breast, doing the dissection of the wall of the chest after the axillary dissection—the reverse of our usual method. In doing the axillary dissection I was unable to palpate any glands except this nodule in the base of the axilla, which had been palpated prior to the operation.

The frozen section showed a cellular medullary carcinoma, and there was no metastasis to the axillary glands.

The patient is now (September 1936) well, almost ten years after operation. This tumor must be looked on as carcinoma in the axillary quadrant of the breast or as carcinoma in aberrant breast tissue in the axilla.

On April 28, 1930, more than three years later, a widow 35 years of age consulted Dr. Bloodgood with a microscopic section from a carcinoma excised from the left breast on Dec. 9, 1929, four and a half months previously. The tumor had been present only one month before it was excised, and it was clinically benign. At the examination Dr. Bloodgood was unable to palpate any nodules in the scar, breast or axilla. He decided to give irradiation, which was carried out from April 28 to May 9.

Dr. Bloodgood decided on irradiation first because he felt that the chief danger was that metastasis had already taken place during the four and one-half month interval since the operation. When the patient returned on October 13, five months later, examination of the breast gave entirely negative results, but a second course of irradiation was given over the breast, axilla and mediastinum. There has been no further operation other than the excision of the tumor, and the patient is now well, six and a half years since the operation.

On Dec. 12, 1931, Mrs. T. consulted us with an operable but very advanced carcinoma of the breast in which there was beginning carcinoma *en cuirasse* (fig. 1 *A*). Figure 1 *B* shows the result three months after irradiation, and the patient is now well, five years after treatment. The only treatment was one course of irradiation. No biopsy was done in this case; so the only evidence that this patient had cancer was clinical.

Preoperative irradiation was not taken up seriously in this clinic until the summer of 1932, four years ago, when Dr. Bloodgood returned from a visit to some of the outstanding radiologic clinics in Europe. At that time I was much opposed to giving a patient with carcinoma of the breast preoperative irradiation and felt that there was a distinct danger in delaying the operation for irradiation, and I believe this is the view of the majority of my colleagues today.

On June 15, 1932, more than four years ago, Mrs. M. J., aged 57, consulted us because of a large, visible mass occupying the entire right breast, producing a dome-shaped bulging of the breast with the nipple at the top of the dome. The mass was adherent to the skin and the nipple, and there was fixation of the nipple and of the areola. In spite of the extensive involvement of the breast, there were no palpable glands in the axilla. The tumor had been present for five months. The patient was referred to the Kelly Hospital for preoperative irradiation. This was carried out by Dr. Edmond Kelly, from whose notes the following information was taken: During June 1932 a total of 8 gram hours of radium treatment was given at a distance of 5 cm. directly to the right axilla with the pack; also 5 gram hours at a distance of 4 cm. to the right lateral aspect of the right breast and similar treatment to the left lateral aspect of the right breast. In addition to this, nine 4.2 millicurie gold needles were implanted permanently into the substance of the breast, scattered equally through its periphery, yielding a total radiation of approximately 4.5 gram hours during the life of the needles (twenty-eight days). The patient was then given 5 gram hours at a distance of 4 cm. to the right supraclavicular space. In addition, she was given high voltage roentgen therapy through a portal 10 by 10 cm., 900 roentgens each to the anterior and the posterior surface of the right axilla.

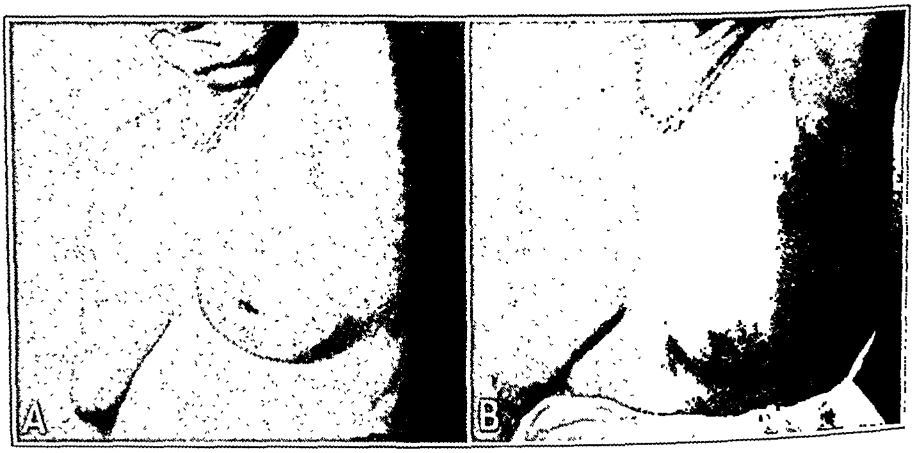

Fig. 1.—*A*, photograph of a patient taken on Dec. 12, 1931, showing an advanced, clinically malignant tumor of the breast. *B*, the same patient on March 23, 1932, after treatment by irradiation only. The patient was still well in May 1936.

The total amount of radiation was given in ten days and was completed on June 25. On September 30, more than three months later, Dr. Bloodgood and I did the operation, which consisted of an exploratory incision (definite cancer was observed in the frozen sections) and the excision of the breast and pectoral muscles but not of the axilla. The axillary dissection was omitted because of the precarious condition of the patient. Figure 2 shows the appearance of the patient before and after operation, and figure 3, the microscopic pathologic picture. The patient is now well more than four years after operation and is our first example of a patient with an operable but advanced carcinoma of the breast who was cured for four years by complete irradiation and incomplete surgical excision.

Later I shall give the figures on excision of the breast only (including dissection of the wall of the chest) with and without preoperative irradiation. The total number of patients in this group is small, and the therapy is not, in my opinion, the treatment of choice. The foregoing case marked the beginning of our intensive study of preoperative irradiation for carcinoma of the breast.

DATA ON CASES OF PRIMARY AND RECURRENT CARCINOMA OF THE BREAST

For the purposes of the present study all cases of primary and recurrent carcinoma of the breast observed in the clinic from January 1931 to December 1935 are included, or, in other words, during the immediate preceding five year period, and while it is clear that any report on such a recent series of cases may be criticized as premature, it was felt that a preliminary report at this time might bring out and emphasize what seems to be the keynote of the problem, which is that there is apparently no danger in delaying the complete operation for one course of preoperative irradiation.

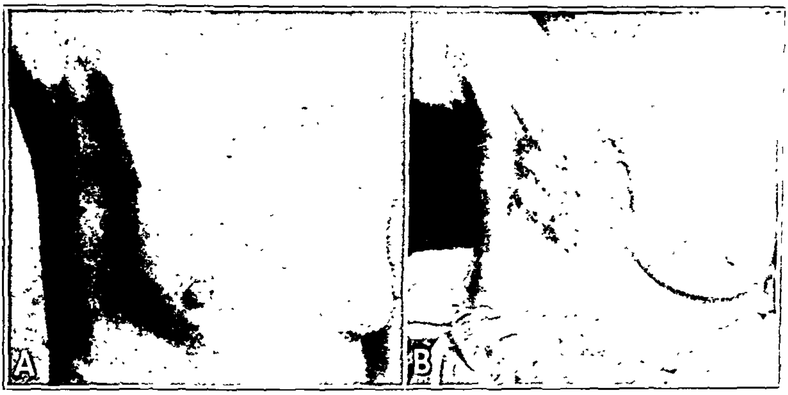

Fig. 2.—*A*, photograph of a patient with a cancer involving the larger part of the breast. *B*, the same patient after operation. (These photographs were previously published by Bloodgood, J. C.: Am. J. Surg. 28:490, 1935.)

A summary of the data to be analyzed is presented in table 1, and while it is realized that the number of patients studied is not large, the numbers in the different groups seem to be near enough equal so as to allow some basis for comparison, and I plan to report on the same series again at the end of five years.

At this writing (September 1936) from four years to nine months has elapsed since therapy in the cases in which irradiation was employed, with one exception, and in the cases in which surgical treatment only was used from two to five years or more has elapsed.

In table 1, the patients in groups 1, 2 and 3 include the majority of those with primary carcinoma, and it is these patients who attract particular attention. When one compares the data in table 2 with those in table 3 one is comparing the results in forty-three patients who were subjected to preoperative irradiation followed by the complete operation with those in fifty-one patients who underwent complete operation without preoperative irradiation. Of the former group, thirty, or 71 per cent, are living and free from recurrence, while of the latter group, only seventeen, or 33 per cent, are living and free from recurrence. While eight of the former group died of cancer and four are living with recur-

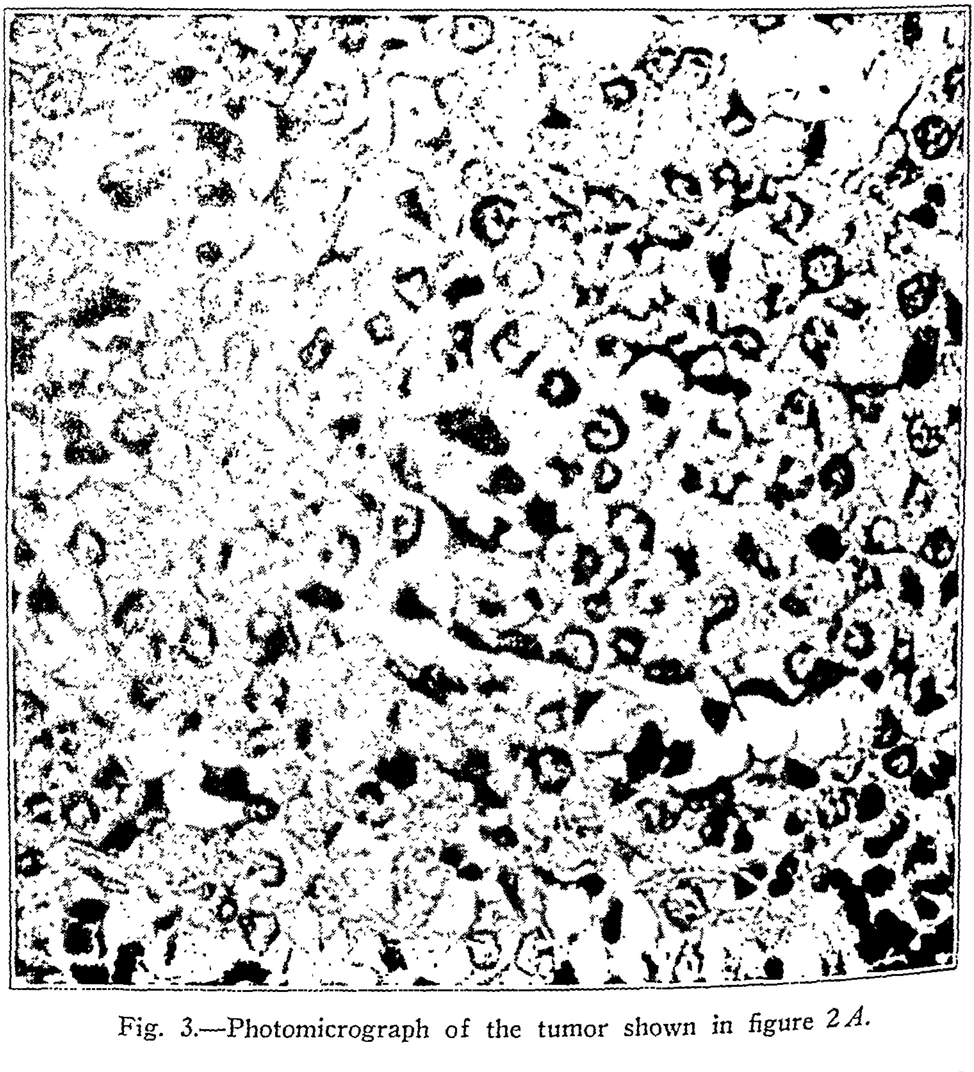

Fig. 3.—Photomicrograph of the tumor shown in figure 2*A*.

rence (28 per cent), twenty-eight of the latter group are dead of cancer and three are living with recurrence (60 per cent).

However, for the group of thirty patients living and free from recurrence after preoperative irradiation followed by the complete operation the average length of time since irradiation was begun is only one year and ten months, whereas for the group of seventeen patients living and free from recurrence after the complete operation only the average length of time since operation is three years and four months. For the group of twelve patients dead or living with recurrence after preoperative irradiation plus the complete operation, the average length of time since irradiation was begun is one year and nine months, and for the group of thirty-one patients dead or living with recurrence after the complete operation only, the average length of time since operation is one year and seven months.

TABLE 1.—*Classification of Patients According to Treatment and Results*

Group	Status	No. of Patients
1	Preoperative irradiation and complete operation	43
2	*Complete operation; no preoperative irradiation*	51
3	Irradiation only, including excision of tumor and biopsy	42
4	Excision of breast only	9
5	Recurrent carcinoma	41
6	Insufficient record	6
	Total	192

If such limited statistics indicate anything, it is interesting to note that there is apparently no evidence that the addition of preoperative irradiation prolongs the duration of life in those persons who are to die of the disease.

It should again be emphasized at this point that the figures and percentages given in tables 2 and 3 and in the subsequent tables are merely the figures and percentages as they have been worked out for the present study and should not be interpreted except in this light. They are not given as proof or even as arguments in favor of preoperative irradiation or that preoperative irradiation followed by the complete operation will cure, for five years or longer, a larger percentage of patients. The solution of this problem, at least as far as this series of patients is concerned, will have to await the passage of time. On the other hand, the reason for the publication of these figures is that sufficient time seems to have elapsed to indicate that there is apparently no danger in delaying the complete operation for one course of preoperative irradiation, provided sufficient time elapses between the irradiation and the operation, and in our experience the optimum time for the operation is from two and a half to three months after the irradiation is completed. This interval allows the skin and deeper structures to return to normal, even though there have been blistering and epitheliitis from the irradiation.

At the beginning we were inclined to operate too soon after completion of the irradiation. The only death occurred in the following case:

The patient consulted us on May 10, 1934, with a section from a tumor which had been removed from her breast six days previously. The section showed medullary carcinoma, and there was a small gland palpable in the axilla. She was given a course of preoperative irradiation from May 10 to May 26. When she returned on July 10, less than two months later, there was a small nodule in the upper end of the scar of two weeks' duration, and for this reason we decided on a second course of irradiation before operating. The second course was begun on July 10 and was completed on July 20, at which time the little nodule that we had felt in the scar ten days previously had entirely disappeared, and the little gland that we had palpated in the axilla on May 10 was no longer palpable. When the patient returned for her next examination, on October 22, there was no evidence of any

Table 2.—*End-Results for Patients in Group 1*

Total number of patients	43	
Living, free from recurrence	30	(71%)
Death from cancer	8	(28%)
Living with recurrence	4	
Death postoperatively, due to infection	1	
Average length of time since irradiation was begun for patients living and free from recurrence	1 yr., 10 mo.	
Average length of time since irradiation was begun for patients dead or living with recurrence	1 yr., 9 mo.	

Table 3.—*End-Results for Patients in Group 2*

Total number of patients	51	
Living, free from recurrence	17	(33%)
Death from cancer	28	(60%)
Living with recurrence	3	
No note	2	
Death from another cause	1	
Average length of time since operation for patients living and free from recurrence	3 yr., 4 mo.	
Average duration of life after operation for patients dead or living with recurrence	1 yr., 7 mo.	

Table 4.—*End-Results for Patients in Group 3*

Total number of patients	42	
Living and well	13	(31%)
Death from cancer	26	(62%)
Lost from observation	2	(7%)
Death from another cause	1	
Average duration of life from onset of tumor (from history) until death	23 mo.	
Average duration of life from time of admission (irradiation) until death	14 mo.	
Average length of time since admission (irradiation) for patients living and well	2 yr., 3 mo.	
Average length of time since onset of disease for patients living and well	2 yr., 8 mo.	

recurrence of the disease in the breast or the axilla. Three months later, at our examination on Jan. 25, 1935. there was another nodule in the scar of one month's duration, and a third course of irradiation was given, from Janury 25 to February 12. On February 15, three days later, I did the complete operation. Sections from the breast and axilla showed no residual cancer. Dr. Gey reported the tissue culture to be negative.

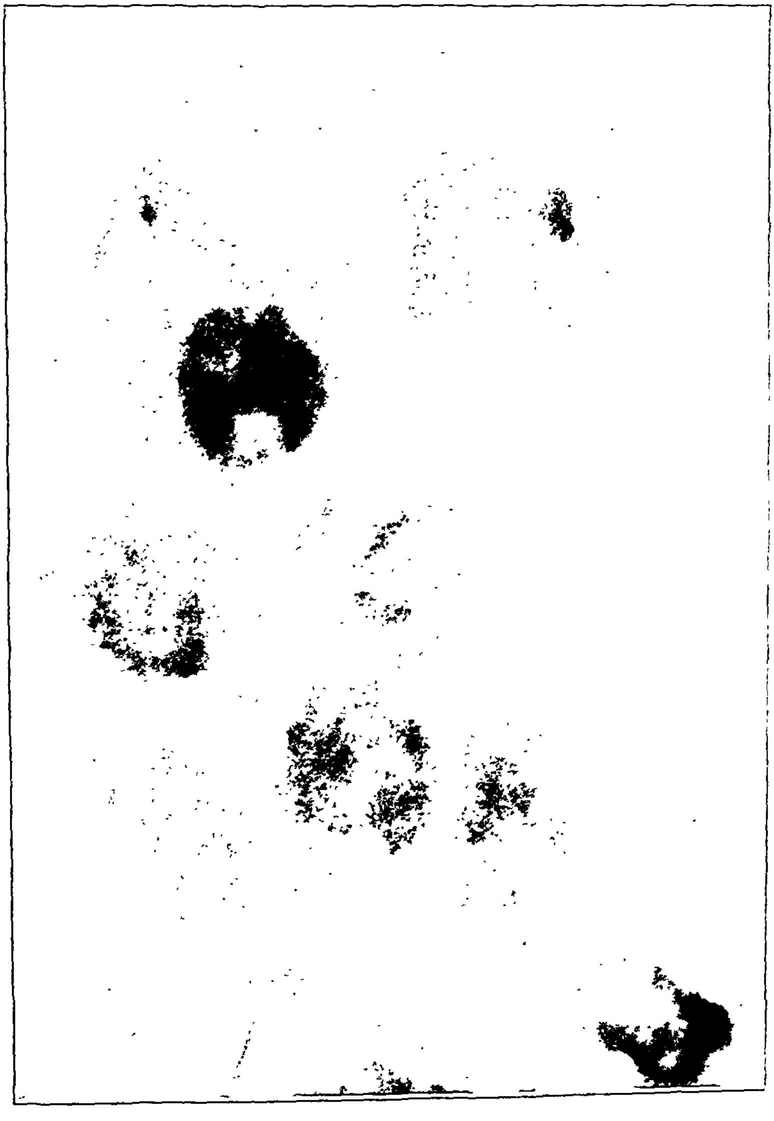

Fig. 4.—High power photomicrograph of a smear made from a biopsy specimen secured by aspiration, showing cells distinctly of the malignant type. (This photograph was previously published by *Bloodgood, J. C.*, and Stewart, G. A.: South. M. J. **29**:651, 1936.)

The wound became infected with hemolytic streptococci, and in spite of our recognizing the infection at once and starting treatment with diluted solution of sodium hypochlorite, the patient died on the tenth day after operation. This is the only infection due to hemolytic streptococci that we have had in a breast wound since the influenza epidemic in 1918, and it is quite possible that it was an accidental occurrence, but I have always felt that the tissues were unable to take care of this infection because they had not yet recovered from the injury of the irradiation.

Of the forty-three patients on whom preoperative irradiation and the complete operation were done, twenty-eight received irradiation without a biopsy because the tumor was clinically malignant, and one patient was treated with irradiation followed by a biopsy and immediately after the biopsy by the complete operation. Biopsy was done for fifteen patients before irradiation, excision of the tumor being done in fourteen instances and aspiration in one instance (fig. 4). Tissue cultures were taken in twenty-three of the forty-three cases and were reported by Dr. Gey as positive in six instances (29 per cent) and negative in fifteen instances (71 per cent). The tissue culture was questionable in two cases (table 5). What the significance of the growth of the tumor or the lack of the growth of the tumor in tissue culture is as yet not known because in the fifty-one cases in which the complete operation was done without preoperative irradiation the tissue culture was taken in only four instances. It was positive twice and negative twice (table 6).

TABLE 5.—*Data Concerning Biopsy and Tissue Culture on Patients in Group 1*

Total number of patients			43
Biopsy			16
Before irradiation		15	
Excision of tumor	14		
Aspiration	1		
After irradiation—followed by complete operation		1	
No biopsy			27
Tissue cultures made			23
Positive	6 (29%)		
Negative	15 (71%)		
Questionable	2		
No cultures made			20

TABLE 6.—*Data Concerning Tissue Culture on Patients in Group 2*

Total number of patients	51
Tissue culture positive	2
Tissue culture negative	2
No culture taken	47
Postoperative irradiation as a routine	9
Postoperative irradiation after recurrence	10

In connection with biopsy, there is one case I shall report a little more in detail because the procedure followed was so unorthodox and brings up the question of what shall be done for a clinically benign tumor which in a frozen section proves to be cancer.

On Nov. 5, 1935, I explored a clinically benign tumor, smaller than a 25 cent piece, of two months' duration, in a woman 46 years of age. After excising the tumor and bisecting it, I was convinced that it was carcinoma, and immediate preparation and study of a frozen section confirmed this. The gross and microscopic pictures are presented in figures 5 and 6. In this case, instead of disinfecting the wound and doing the complete operation, I simply closed the wound and referred the patient to Dr. Neill for irradiation, which was started at once to the supraclavicular area and axilla; after about one week, during which time the wound in the breast healed, the irradiation was carried over the breast. Figure 7 is the photograph of the patient after irradiation.

Fig. 5.—Photograph of the gross specimen of a clinically benign tumor.

On Jan. 21, 1936, three months later, I did the complete operation (fig. 8). There was no metastasis to the axillary glands, and there was no residual carcinoma in the breast. A culture of tissue from the tumor was positive, and one was also reported to be positive after the complete operation.

The chances of curing a patient with a tumor like this for five years by surgical measures alone are 70 per cent, and it remains to be seen whether the addition of this preoperative irradiation will increase or decrease the chances of a cure.

Of the forty-three patients subjected to preoperative irradiation and the complete operation, we found no residual cancer in the breast or axilla in ten (24 per cent), and of these ten, biopsy was performed for seven. We found residual cancer in the breast or axilla of thirty-two patients (76 per cent), as shown in table 7. These figures should be compared with those of Adair and Stewart.

The factors which seem to influence the prognosis are the grade of malignancy of the tumor (Broders), the presence or absence of glandular involvement and the extent of the involvement. The grade of the tumor is really an index of the rapidity of the growth, whereas the involvement of the axillary glands is an index of the extent of the growth and depends to some extent on the grade, but perhaps more on the duration of the tumor. I shall take up the question of involvement of the glands first (tables 8 and 9). Of the group of forty-three patients on whom preoperative irradiation and the complete operation were done, the glands were involved in eighteen (44 per cent) and showed no metastasis in twenty-three (56 per cent). Of the group with no metastasis to the axillary glands, twenty-one are well (91 per cent), one died of cancer and one died of some other cause. Of the eighteen patients in whom the glands were involved, eight (44 per cent) are well and ten (56 per cent) died of cancer (table 8).

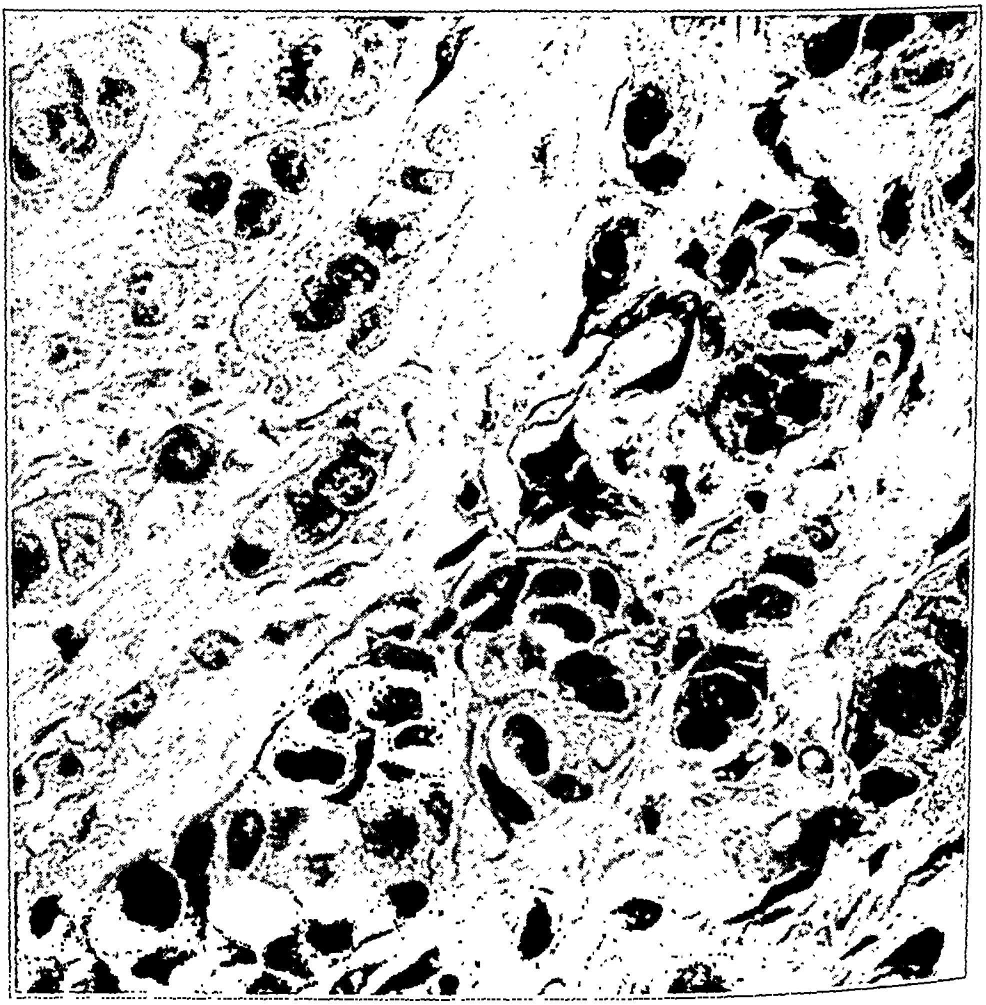

Fig. 6.—Photomicrograph of a clinically benign tumor.

Of the group of fifty-one patients subjected to the complete operation but without preoperative irradiation, there was no metastasis to the axillary glands in fourteen (30 per cent).

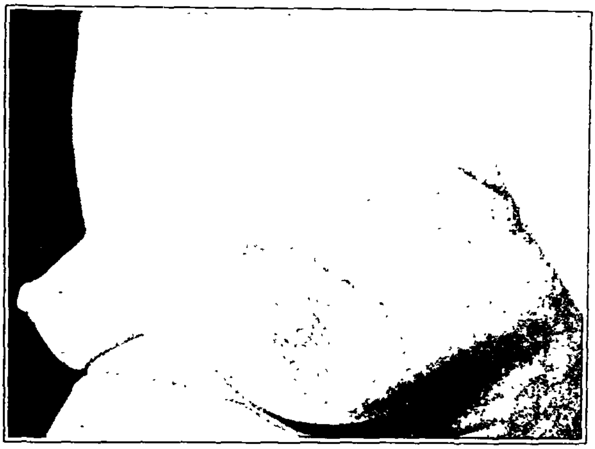

Fig. 7.—Photograph of a patient after excision of the tumor and irradiation. For the gross and microscopic appearance of the tumor see figures 5 and 6.

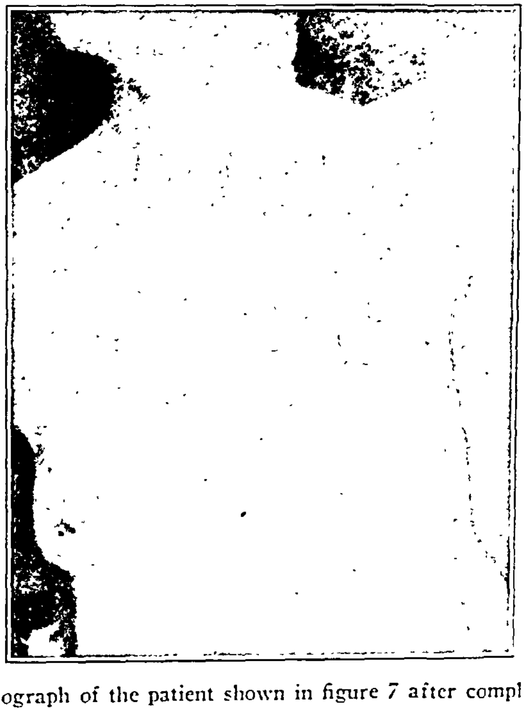

Fig. 8.—Photograph of the patient shown in figure 7 after complete operation.

Frequently I have been able to palpate axillary glands prior to irradiation and three months later prior to operation all evidence of palpable axillary glands had disappeared; it seems quite possible that the irradiation is responsible for the higher percentage of patients free from axillary involvement—56 per cent in the group treated by irradiation as compared with 30 per cent in the group on whom irradiation was not done. From tables 8 and 9, it is seen that 91 per cent of the patients who were free from involvement of the glands were well after preoperative irradiation and the complete operation and that 90 per cent of those without metastasis to the glands were well after complete operation only; so there is no evidence yet that irradiation is of value in early cases of cancer in which there is no involvement of the axillary glands, but there is no evidence that it is harmful, even though it may be unnecessary. On the other hand, 44 per cent of the patients with metastasis to the glands who were subjected to preoperative irradiation plus complete operation were well, as compared with 24 per cent of those who were treated with complete operation alone. It is to be emphasized, however, that the patients who received irradiation on the average have been treated more recently than those who were not treated by irradiation.

TABLE 7.—*Data Concerning Residual Cancer in Patients in Group 1*

Total number of patients		43	
No residual cancer in breast or axilla		10	(24%)
Biopsy, consisting of excision of tumor	7		
No biopsy	2		
Sections unsatisfactory	1		
Residual cancer in breast or axilla		32	(76%)
No note		1	

TABLE 8.—*End-Results in Relation to Metastasis in Patients in Group 1*

Total number of patients		43	
No metastases to glands		23	(56%)
Well	21 (91%)		
Death from cancer	1		
Death from another cause	1		
Metastases to glands		18	(44%)
Well	8 (44%)		
Death from cancer	10 (56%)		
No note		2	

TABLE 9.—*End-Results in Relation to Metastasis in Patients in Group 2*

Total number of patients		51	
No metastasis to glands		14	(30%)
Well	9 (90%)		
Death from cancer	1 (10%)		
Death from another cause	1		
No record	3		
Metastasis to glands		33	(70%)
Well	8 (24%)		
Death from cancer	25 (76%)		
No note		4	

When only the glands at the base of the axilla are involved, the complete operation alone offers about 25 per cent chances of a five year cure. In the cases included in this report, which I have already stated is not a report of five year cures, there were seven patients on whom the complete operation without preliminary irradiation was done in whom only the glands of the base of the axilla showed metastasis, and of these seven only two are well (29 per cent) and five are dead of cancer (71 per cent). In the group on whom preoperative irradiation plus the complete operation was done, there are six in whom only the glands of the base of the axilla showed metastasis, and of these, four (66.6 per cent) are well. The actual number of patients with involvement of the glands of the base and the middle of the axilla or of the base, the middle and the highest apex of the axilla is greater in the group who did not receive irradiation, but the number of patients in each group is too small to allow any conclusions (tables 10 and 11).

TABLE 10.—*End-Results in Relation to Extent of Metastasis in Patients in Group 1*

Total number of patients		43
Glands plus		18 (44%)
Well	8 (44%)	
Death from cancer	10 (56%)	
Gland 1 plus		6
Well	4 (66.66%)	
Death from cancer	2 (33.33%)	
Glands 1, 2 plus		1 well
Glands 1, 2, 3 plus		8
Well	1 (12.5%)	
Death from cancer	7 (88.5%)	

TABLE 11.—*End-Results in Relation to Extent of Metastasis in Patients in Group 2*

Total number of patients		51
Glands plus		33 (70%)
Well	8 (24%)	
Death from cancer	25 (76%)	
Glands 1 plus		7
Well	2 (29%)	
Dead	5 (71%)	
Glands 1, 2 plus		6
Well	1 (17%)	
Death from cancer	5 (83%)	
Glands 1, 2, 3 plus		12
Well	2 (17%)	
Death from cancer	10 (83%)	

Tables 12 and 13 are compiled to show the ultimate result according to the microscopic grading of the tumor in the forty-three patients on whom preoperative irradiation and the complete operation were done and in the fifty-one on whom the complete operation was performed but no preoperative irradiation was given. Of the patients in the first group, 75 per cent with a tumor of grade 1 or grade 2 are well and

25 per cent died of cancer, whereas of those in the second group, 70 per cent are well and 30 per cent died of cancer, an insignificant difference in the percentages. Sixty-one per cent of the patients with tumors of grade 3 who were given irradiation are well, as against 23 per cent of the patients with this grade of tumor who were not given irradiation. The number of patients with a tumor of grade 4 in both groups is too small to be of any value in this study. From these figures it would seem that if there is any value in preoperative irradiation it is for the tumor of grade 3.

TABLE 12.—*End-Results in Patients in Group 1 in Relation to Grade of Tumor*

Total number of patients		43
Grade 1 tumor		48
Well	6 (75%)	
Death from cancer	2 (25%)	
Grade 2 tumor		12
Well	9 (75%)	
Death from cancer	3 (25%)	
Grade 3 tumor		18
Well	11 (61%)	
Death from cancer	7 (39%)	
Grade 4 tumor		2
Well	1	
Death from another cause	1	
No residual cancer		2
Sections unsatisfactory		1

TABLE 13.—*End-Results in Patients in Group 2 in Relation to Grade of Tumor*

Total number of patients		51
Grade 1 tumor		None
Grade 2 tumor		13
Well	7 (70%)	
Death from cancer	3 (30%)	
Death from another cause	1	
No note	2	
Grade 3 tumor		27
Well	6 (23%)	
Death from cancer	20 (77%)	
No note	1	
Grade 4 tumor		2
Well	1 (50%)	
Death from cancer	1 (50%)	
No note		9

In this series of one hundred and ninety-two patients it has already been noted that there were forty-two with primary carcinoma on whom irradiation only or excision of the tumor or some other type of biopsy plus irradiation was performed (table 4). Up to the present time irradiation has not been advised as the only treatment in any case of primary operable carcinoma of the breast except to a few patients over 70 years of age in whom the tumor was arrested by irradiation and to two younger women with acute carcinoma, and in these all evidence of the tumor in the breast and axillary glands disappeared rapidly under irradiation.

Of this group of forty-two patients, thirteen had clinically operable tumors. Two of these were the young women with acute carcinomas, and the remaining eleven were older women. There were a few patients in this group who refused the complete operation. Of the thirteen with operable tumors who were given irradiation only, 66 per cent are well (table 14). As the tumor and axillary glands disappeared so rapidly under irradiation in the two patients with acute carcinoma, we decided not to operate because we felt that the chief danger was distant metastases and that should the tumor recur in the breast or axillary glands we could always operate. These patients were kept under constant observation. One of the patients died of cancer one year and eight months after the beginning of irradiation, but there was no recurrence in the breast or axilla until two months before death, at which time she was bedridden because of metastases to the pelvis, lower lumbar vertebrae and chest. The other patient is well and free from clinical evidence of cancer one year and two months after irradiation began, during which period there have been two courses of irradiation.

TABLE 14.—*End-Results in Patients in Group 3*

Total number of patients		42
No biopsy		29
Biopsy		13
Excision of tumor	8	
Clinically operable tumors		13
Well	8 (66%)	
Average duration of time since admission (irradiation)		2 yr., 3 mo.
Death from cancer	4 (33%)	
Average duration of life after irradiation		1 yr., 8 mo.

TABLE 15.—*End-Results in Patients Subjected to Excision of the Breast Only*

Total number of patients		9
No recurrence		4
Average duration of time since operation	3 yr., 3 mo.	
Death from cancer		4
Average duration of life since operation	2 yr.	
Death from other cause		1
Duration of life after operation (no recurrence)	2 yr., 11 mo.	

The other twenty-nine patients who received irradiation only had clinically inoperable tumors, so there was no choice in treatment other than irradiation. It has already been noted in table 4 that 31 per cent of these patients are well and that the average period of time since irradiation was begun is two years and three months.

One of the reasons for publishing this material at this time as a preliminary report is that there is such a great difference of opinion between radiologists of experience and surgeons of experience. Some radiologists feel that carcinoma of the breast is no longer a surgical problem and that the treatment should be left entirely to the radiologists. They strongly object to the complete operation but occasionally agree to a simple mastectomy. On the other hand, the majority of surgeons of experience have not accepted as yet preoperative irradiation and feel that the best results at present can be obtained by the complete operation or by the complete operation and postoperative irradiation.

My associates and I have had a very limited experience in this clinic with excision of the breast only and have taken the point of view that it is an illogical operation in most instances because it is too much of an operation for a benign lesion and not enough of an operation for cancer. In this series there are nine patients who were subjected to excision of the breast only or excision of the breast and pectoral muscles but not the axillary dissection. Of these nine, four are well, four died of cancer and one died of another cause. The average length of time after operation in the four patients who are well is two years and eleven months (table 15). Of these nine patients, four received preoperative irradiation, and three are well (tables 16 and 17). The average length of time since irradiation was begun is three years and five months. There were five patients in the group of nine who received no preoperative irradiation (tables 17 and 18). One patient is well two years and seven months after operation, three died of cancer (average duration of life since irradiation, three years) and one died of another cause in two years and eleven months without any clinical evidence of recurrence of metastases.

TABLE 16.—*Results in Patients Subjected to Preoperative Irradiation Followed by Excision of the Breast*

Total number of patients		4
Well, *no recurrence*		3 (75%)
Average duration of time since irradiation	3 yr., 5 mo.	
Death from cancer		1
Duration of life after irradiation	5 mo.	
Duration of life after operation	2 mo.	

From these figures alone, which of course are limited, there is no actual proof that preoperative irradiation followed by simple excision of the breast is not as good as preoperative irradiation followed by the complete operation, yet if the reader will refer again to table 8 he will find that 44 per cent of the patients who had preoperative irradiation followed by the complete operation had demonstrable metastases in the axillary glands, and personally I feel very strongly that there should be no restriction of the complete operation because of preoperative irradiation.

The surgeon will have one opportunity only to cure a patient with carcinoma of the breast. When a clinically benign tumor proves in a frozen section to be cancer or is suggestive of cancer, he has the choice of doing the complete operation at once or closing the wound, giving preoperative irradiation and after the proper interval of time doing the complete operation. In the doubtful cases, while the irradiation is going on the section can be submitted to other pathologists for their opinions. When the sections show cancer, even though all palpable evidence of disease was completely removed for biopsy, for the present anyway, I still feel that the complete operation should follow.

TABLE 17.—*Data on Patients Subjected to Excision of Breast Only in Regard to Grade of Tumor and Tissue Culture*

Total number of patients		9
Number of patients subjected to preoperative irradiation		4
Well (tumors, grade 1, 2, 2)	3	
Death from cancer (grade 3)	1	
No preoperative irradiation		5
Well (tumor, grade 3)	1	
Death from cancer (grade 2, 3 and no tissue from 1)	3	
Lost from observation (no tissue)	1	
Tissue culture		2
Negative (preoperative irradiation)	1	
Inaccurate (preoperative irradiation)	1	

TABLE 18.—*End-Results in Patients Subjected to Excision of Breast Without Preoperative Irradiation*

Total number of patients		5	
Well, no recurrence		1	(25%)
Duration of time since operation	2 yr., 7 mo.		
Death from cancer		3	(75%)
Average duration of life after operation	3 yr.		
Death from other cause		1	
Duration of life after operation	2 yr., 11 mo.		

TABLE 19.—*End-Results for Patients in Group 5*

Total number of patients		41	
Well		4	(9%)
Average duration of time since admission to clinic	1 yr.		
Death from cancer		36	(88%)
Average duration of life after admission to clinic	1 yr., 4 mo.		
Death from another cause (suicide)		1	(2%)

The chances of curing a recurrent carcinoma of the breast are so small that I have about decided no longer to advise operation. Of the forty-one patients with recurrent carcinoma in this series, only four (9 per cent) are well, and the average length of time since these four were admitted to the clinic is only one year (table 19). Some of these recurrent carcinomas will be operable and present an apparently favorable prognosis, but the fact alone that they are recurrent almost excludes any possibility of a cure by surgical measures or by preoperative irradiation and surgical treatment. Perhaps even in this group it may be wise to treat by irradiation only.

GASTRIC SURGERY AND GASTROSCOPY

DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT LESIONS; OPERABILITY OF TUMORS AS DETERMINED BY GASTROSCOPY; EARLY DIAGNOSIS OF GASTRIC CARCINOMA; THE POSTOPERATIVE STOMACH

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The purpose of this paper is to show the usefulness and value of gastroscopy to the surgeon.[1] The following questions will be discussed: 1. Is a lesion of the stomach, which has been diagnosed by other methods, a benign ulcer or a carcinoma? 2. Is cancer of the stomach operable or not? 3. Of what value is gastroscopy in the early diagnosis of carcinoma, and may it improve the operative results? 4. What are the reasons for the abdominal distress which so frequently follows operations for gastric lesions?

We shall not include the results of the numerous gastroscopies carried out by one of us (R. S.) in Germany, because the records cannot be controlled. Thus we shall restrict ourselves to the gastroscopic examinations carried out at the Billings Hospital of the University of Chicago Clinics.[2] The majority of the patients were referred for gastroscopy by Dr. W. L. Palmer, chief of the gastro-intestinal department. A total of four hundred and sixty-five gastroscopies were performed; forty-one of the patients on whom gastroscopy was per-

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All surgical work was done by the Surgical Department of the University of Chicago Clinics unless otherwise stipulated. Splendid cooperation was given by the Department of Radiology (Dr. Hodges).

[1] Schindler, R.: Lehrbuch und Atlas der Gastroskopie, Munich, J. F. Lehmanns, 1923; Diagnostic Gastroscopy, with Special Reference to the Flexible Gastroscope, J. A. M. A. **105**:352-355 (Aug. 3) 1935; A New Tube for Anaesthetization of the Hypopharynx, Am. J. Digest. Dis. & Nutrition **2**:281-282 (July) 1935; Gastroscopy in Thirty Cases of Gastric Neoplasm, Arch. Int. Med. **32**:635-646 (Oct.) 1923. Moutier, F.: Traité de gastroscopie et de pathologie endoscopique de l'estomac, Paris, Masson & Cie, 1935.

[2] The flexible Schindler-Wolf gastroscope was used in all examinations. This instrument may be obtained from the Zeiss Corporation, 485 Fifth Avenue, New York.

formed also received surgical treatment, and it is this group which furnishes the material for our paper. Biopsic control was possible in twenty cases; the remaining twenty-one are presented because of the interesting observations which they offer. Since more than one gastroscopy was done on many of our patients, a total of seventy-eight gastroscopies were performed on our group of forty-one patients. We realize that complete presentations of such a large amount of material tends to make the paper rather detailed, but since so little work has been done relative to the value of gastroscopy in cases involving operations for gastric lesions, we believe that surgeons will appreciate these details as being valuable for purposes of study.

A. GASTRIC ULCER AND CARCINOMA VISUALIZED BY GASTROSCOPY BEFORE OPERATION

DIFFERENTIAL DIAGNOSIS

Benign Ulcer.—The difference between a benign and a malignant pyloric obstruction is characteristic gastroscopically, although it is well known that a duodenal ulcer cannot be seen with the gastroscope. Recent statistics indicate that a prepyloric ulcer is very rare and is generally carcinomatous. We have never seen one gastroscopically, but since the lesser curvature of the antrum is infrequently seen with the gastroscope, this observation is of less importance than is the experience of the pathologist and the surgeon. It is, however, sometimes difficult even for the pathologist to decide, in the gross specimen, whether a pyloric obstruction is benign or malignant. In all instances of carcinomatous obstruction of the pylorus the protruding carcinomatous tissue was seen by gastroscopy, whereas in cases of ulcer of the pyloric channel or of benign pyloric obstruction the pylorus was usually *not* seen because adhesions draw it backward so as to remove it from the field of vision. It may be mentioned that in cases of uncomplicated duodenal ulcer the pylorus is *often* seen very well, and its activity shows no deviation from the normal. The following case illustrates the uncertainty of diagnosis in many of these cases as well as the difficulty of deciding definitely the nature of the lesion by examination of the gross specimen.

Case 1.—*History.*—A white Canadian man aged 38, seen on Aug. 14, 1934, had suffered from epigastric distress for one year without remission. He had lost 35 pounds (15.9 Kg.) in weight and had a sensation of tenderness and fulness which became so acute at times that he felt he would burst. When he induced vomiting, he obtained relief. The vomitus practically always contained undigested food. At no time were tarry stools noted, and there were no other complaints.

Physical Examination.—There was some tenderness in the epigastrium. A large peristaltic wave was seen which moved across the entire upper two thirds of the abdomen. No definite mass was felt. The other organs were normal.

Laboratory Examination.—One thousand, two hundred cubic centimeters of gastric fluid obtained after an Ewald test meal showed: free acid, 37; total acid, 59; lactic acid, 0, and blood, a trace. Microscopic examination of the contents gave normal results. The reaction of the stools to the benzidine test for blood varied from negative to 3 plus.

Roentgen Examination.—The roentgenogram was very suggestive of carcinoma of the antrum of the stomach, with obstruction, retention and dilatation. The condition was thought to be carcinoma of the antrum, but the possibility of an ulcer could not be ruled out.

Gastroscopy.—The stomach contained considerable fluid, which covered the greater curvature. The antrum was well seen, however, particularly in its greater curvature. The pylorus was not completely visible. The mucous membrane was somewhat moist and swollen, but there was no tumor visible; the musculus sphincter antri was very prominent. The mucosa of the body showed no pathologic changes. The gastroscopic diagnosis was gastritis of the antrum.

Clinical Impression.—On the basis of the clinical picture the condition was thought to be carcinoma of the stomach with pyloric obstruction.

Operation (August 20).—The stomach was found to be greatly enlarged, and a hard inflammatory mass was felt at the pylorus. The pyloric antrum and the first part of the duodenum were resected. The duodenum and the end of the stomach were closed, and a posterior gastro-enterostomy was performed with the first part of the jejunum.

Pathologic Examination.—The base of the ulcer was necrotic and yellow and extended well into the wall of the stomach. There were radiating fibrous strands and adhesions about its outer aspect in which there were palpable lymph nodes indicating carcinomatous invasion. Section of the wall showed it to be thickened and to contain translucent and fibrous material. Microscopic examination of the ulcer showed it to be benign.

The diagnostic course of this case is typical. A definite obstruction of the pylorus gave the clinical impression that a carcinoma was present; roentgen examination also indicated carcinoma, although the roentgenologist stated that a benign ulcer could not definitely be ruled out. The surgeon, however, thought that the lesion which he removed was benign, but on gross examination it was thought to be carcinomatous. Microscopic examination proved that the lesion was a benign ulcer. Since no tumorous tissue was seen at the pylorus on gastroscopic examination, we were safe in concluding that carcinoma was not present but that the obstruction was due to a benign lesion with secondary inflammation of the mucosa of the antrum.

After the operation gastroscopy was done three different times. The results will be discussed in section B.

The following case presents a general agreement concerning the nature of the lesion.

Case 2.—*History.*—A man aged 47, seen on Oct. 9, 1934, stated that he had had complaints referable to the stomach for the past seventeen years with rather frequent vomiting but no pain. The past few years he had suffered from distention, which had been relieved by sodium bicarbonate. The appetite had remained good, although the patient had lost 25 pounds (11 Kg.) in the past year and a half.

Physical Examination.—Nothing abnormal was found.

Laboratory Examination.—Two hundred and thirty cubic centimeters of gastric fluid obtained after an Ewald test meal showed: free acid, 40; total acid, 94, and blood, 0. The stools gave a 4 plus reaction to the benzidine test for blood.

Roentgen Examination.—The roentgenogram showed a stenosing ulcer of the pyloric channel with a surrounding inflammatory reaction and resulting gastric retention. Early pyloric neoplasm could not be absolutely ruled out.

Gastroscopy.—The entire stomach, including the pylorus, was well seen. There were no pathologic changes present.

Clinical Impression.—On the basis of the clinical picture the condition was thought to be a duodenal ulcer with high grade stenosis.

Operation (December 8).—Operation was delayed because of the indecision of the patient. A large duodenal ulcer was found which produced almost complete pyloric stenosis. The lesion was situated on the posterior wall about 3 cm. distal to the pylorus. A posterior gastro-enterostomy was performed. No pathologic examination was possible. The patient returned to the clinic on Feb. 4, 1935; he had gained 5 Kg. and looked extremely well.

Although this case was evidently one of obstructive duodenal ulcer, a neoplasm could not be ruled out with certainty by roentgen examination, whereas the gastroscopic examination was conclusive, since the pylorus was well seen and no carcinomatous changes were visualized.

There was complete agreement in diagnosis of the following case.

Case 3.—*History.*—A man aged 67 had suffered from pain in the epigastrium below the xiphoid process for the past twenty-five years, with restlessness, irritability and fatigue becoming prominent during the past two years. There was a loss of weight of 10 pounds (4.5 Kg.) during the past six months.

Physical Examination.—A mass was felt in the epigastrium above the umbilicus that moved with peristaltic waves, which were both visible and palpable.

Roentgen Examination.—The roentgenogram showed high grade pyloric obstruction, thought almost certainly to be the result of a chronic duodenal ulcer.

Gastroscopy.—It was difficult to find the pylorus, but finally the entire antrum and the lower half of the pylorus were well seen. The lower parts of the greater curvature were edematous, as were other parts of the stomach to a lesser degree. In the upper parts of the body red spots were seen. The diagnosis on the basis of the gastroscopic findings was superficial edematous gastritis.

Operation.—The wall of the stomach was found to be markedly thickened. There was definite scarring of the duodenum just beyond the pylorus. A posterior gastro-enterostomy was done, and the patient made an uneventful recovery.

The gastroscopic findings were typical of benign obstruction, especially the high grade edema of the antrum, which is seen only in this condition.

In the differential diagnosis of gastric ulcer other signs are important. It is frequently impossible to differentiate such an ulcer from a carcinoma even in the gross specimen, and one may think that it is just as

EXPLANATION OF PLATE

A, gastroscopic picture of the penetrating benign ulcer of the lesser curvature of the stomach in case 4. The edge of the crater-like ulcer is sharp, and the cardiac part of its floor is brownish. Blood is shown oozing from the lowest part of the floor and accumulating in the dependent part (upward in the picture). The adjacent mucosa is excessively swollen and inflamed. Compare this illustration with figures 1, 2, 3 and 4.

B, gastroscopic picture of the infiltrating carcinoma with ulceration in the case in which operation was not performed. In the center of the picture there is a dark red ulceration. All the other parts of the stomach visualized with the gastroscope were stiff and infiltrated, and the surface was necrotic. The necrosis extended up to the cardia. Compare this illustration with figure 8. Gastroscopy proved immediately the inoperability of the tumor.

C, gastroscopic picture in case 7, showing ulcerative carcinoma. The ulcer is filled with brown clotted blood. The gray ridge discloses the malignant character of the ulcer.

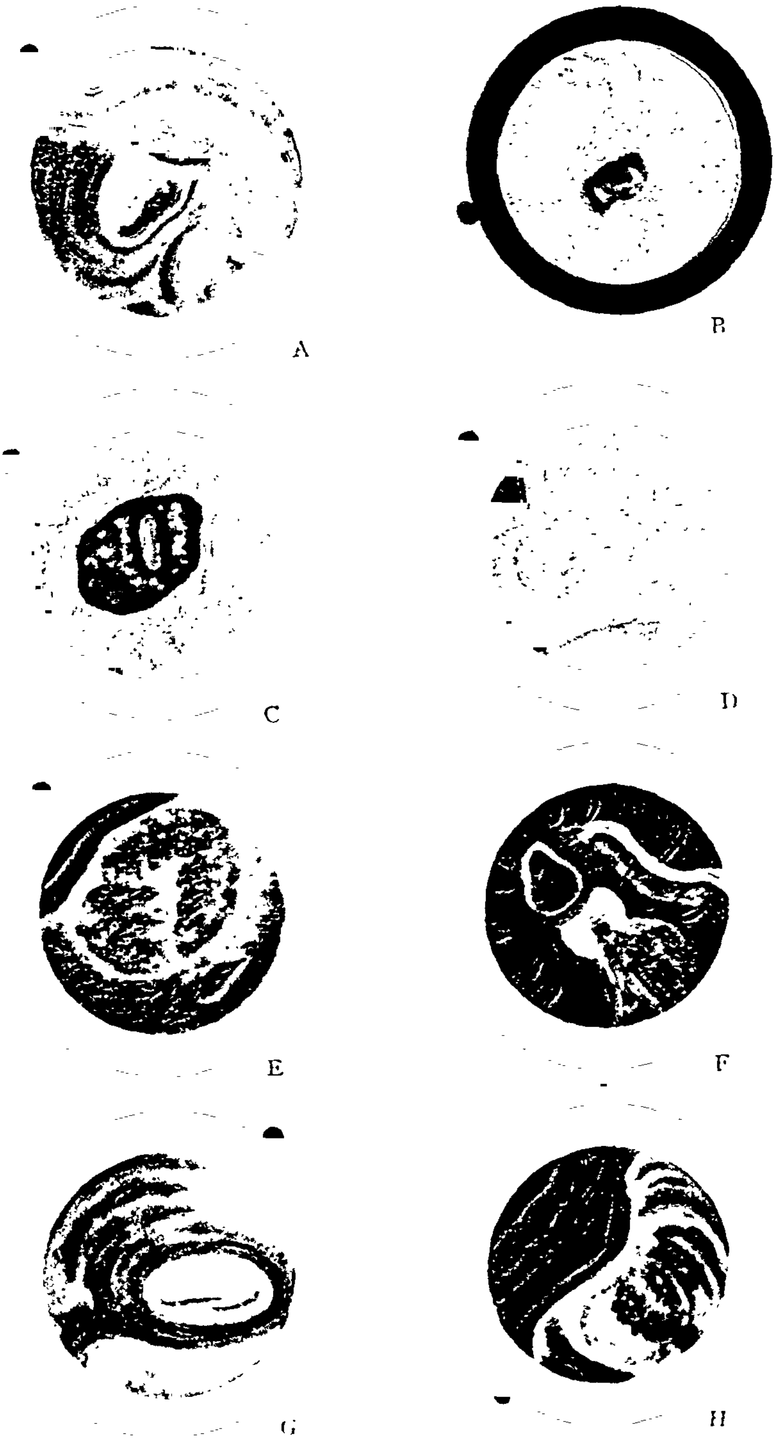
D, gastroscopic picture, also from case 7, made four weeks after *C.* The ulcer as well as the niche (fig. 5) were shallower, but at the pyloric side a nodular infiltration was seen. Compare this picture with figures 6 and 7.

E, gastroscopic picture in case 13, showing an ulcerated carcinoma around the pylorus with a sharply limited wall. The fold above the tumor is the "angulus." The whitish areas are remainders of food. Radical operation was possible. Compare this picture with figures 9 and 10.

F, gastroscopic picture in case 14, showing the patent gastro-enterostomy opening in the center. Intestinal juice flows into the stomach. At the side of the stoma there is a white ulcer larger than the stoma. A silk suture is seen coming out of the mucosa and hanging freely into the cavity of the stomach.

G, gastroscopic picture in case 21, showing the opening phase of the gastro-enterostomy stoma. The objective of the gastroscope is turned toward the anterior wall; the pylorus, which is well seen in figure 12, is not visible. The circular Kerkring folds of the jejunum are seen.

H, gastroscopic picture in case 26, showing a considerable portion of the jejunum in the right lower quadrant. About 2 cm. below the margin a crater-like deep ulcer is seen. The margin is partly covered with pus, and about it mucosal hemorrhages are seen.



PLATE

difficult by gastroscopic examination. This is definitely not so. As a rule these ulcers are seen distinctly gastroscopically, and the circulating blood makes the coloring quite characteristic. It can be further observed that the edge of a carcinoma is never as sharp as it appears to be in the gross specimen after resection and also that the floor of a carcinomatous ulcer blends gradually with the surrounding mucous membrane. If the edge is entirely sharp the lesion may be diagnosed as a benign ulcer; if the edge is not so sharp and the floor is ragged, dirty and irregular, it may safely be called a malignant ulcer. The sharpness of the wall is a more important differential point than is the abnormality of the floor of the lesion.

Case 4.—*History.*—A man aged 51, seen on Oct 24, 1934, about five years previously had an attack of epigastric distress which was thought to be the result of a peptic ulcer. He was placed on the Sippy diet, and the pains disappeared. About one month before he vomited and felt very weak. He placed himself on a milk diet, during which time his distress continued, and his emesis occurred at least twice daily. He had lost 24 pounds (10.9 Kg.) in weight during the past two months.

Physical Examination.—Moderate tenderness was felt in the epigastrium. All other findings were normal.

Laboratory Examination.—One hundred and sixty-five cubic centimeters of gastric fluid obtained after an Ewald test meal showed: free acid, 35, and total acid, 51. Microscopic examination of the contents gave normal results. The stools gave a 4 plus reaction to the benzidine test for blood.

Roentgen Examination (October 26).—There was an enormous penetrating ulcer at the lesser curvature of the stomach; the film showed the thickened gastric rugae of the opposite wall. The size of the lesion and the mucosal changes indicated, but did not prove, the possibility that the ulcer might be carcinomatous (fig. 1).

First Gastroscopy (October 30).—On the lesser curvature of the stomach a large ulcer was seen just above the angulus. It was very deep, and its edges were sharp and undermined. The color of that part of the floor which lay toward the cardia was reddish brown, whereas that near the pylorus was whitish gray. In this region of the ulcer fresh light red blood was oozing from the base and flowed toward the cardiac side of the floor; the mucous membrane of the stomach in this region was definitely spotted. Slightly nearer the cardia the mucous membrane of the anterior wall appeared swollen; it did not reflect light and appeared to be divided into sections by small creases. The entire lower parts of the anterior wall also presented these changes and further disclosed one rather large hemorrhage. On the other hand, all portions of the greater curvature of the posterior wall and of the upper parts of the anterior wall were normal. On the basis of the gastroscopic findings a diagnosis was made of (1) deep bleeding benign ulcer of the lesser curvature of the body above the angulus and (2) marked hypertrophic hemorrhagic gastritis of the anterior wall. (See *A* in the color plate.)

Second Gastroscopy (November 19).—The ulcer was instantly seen. It had lost much of its depth but was still large. Its edge was quite sharp, and the floor was dirty gray. Whitish membranes passed from the mucous membrane of the cardiac side of the ulcer to its floor. The antrum and pylorus were normal. The hypertrophic gastritis of the anterior wall was as distinctly seen as at the last examination and showed no improvement. The other parts of the stomach were normal (fig. 2).

Fig. 1 (case 4).—Roentgenographic picture of the stomach. Because of the size of the niche, the diagnosis of a malignant growth could not be ruled out. Compare this picture with the gastroscopic picture in *A* of the color plate. Gastroscopically, the benign nature of the lesion was evident.

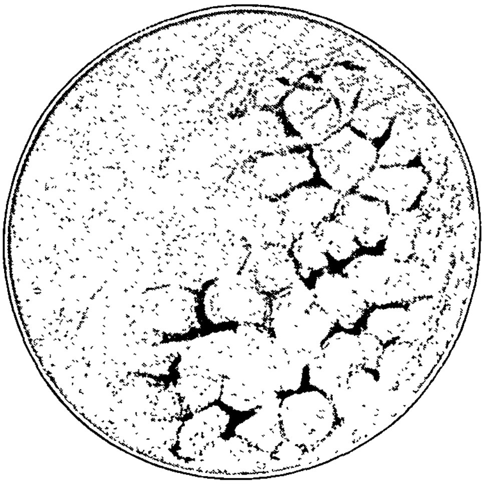


Fig. 2 (case 4).—Severe hypertrophic gastritis in the vicinity of the ulcer, as visualized gastroscopically. The mucous membrane is swollen and nodular ("cobblestone formation"), and hemorrhage is seen (see left side of illustration). (From Schindler, R.: Am. J. Digest. Dis. & Nutrition **2:**655 [Jan.] 1936.)

Second Roentgen Examination (November 26).—There was no diminution in the size of the large penetrating ulcer of the lesser curvature of the stomach.

Clinical Impression.—Considering the history of symptoms of long standing, the ulcer was believed to be benign. The patient was advised to have an operation

Operation (November 30).—A large ulcer was found situated high on the lesser curvature. Its crater was large enough to admit the tip of a thumb. Gastric resection was done, with uneventful recovery.

Pathologic Examination.—About 5 cm. above the pylorus there was a deep penetrating ulcer, measuring 2.75 by 2 cm., with a sharply defined border and a punched-out appearance. The edges were slightly undermined. The base consisted of adhesive omental tissue. The rugae which radiated from the ulcer were much flattened for an area 8 cm. in diameter around the lesion. This region appeared hyperemic, swollen and hypertrophic (fig. 3). The border of the ulcer was raised and indurated but was not stony hard. The rest of the mucosa appeared practically normal except for petechiae. Section through the edge of the crater of the ulcer showed an ulcer penetrating through all walls of the stomach; the floor was flat and composed of fibrosed omentum, whereas the sides were steep and abrupt. Round cell and eosinophilic infiltration was seen involving the fibrosed omentum and the wall of the stomach. Sections from various other parts of the stomach showed varying degrees of eosinophilia and polymorphonuclear invasion but no evidence of ulceration or malignancy (fig. 4).

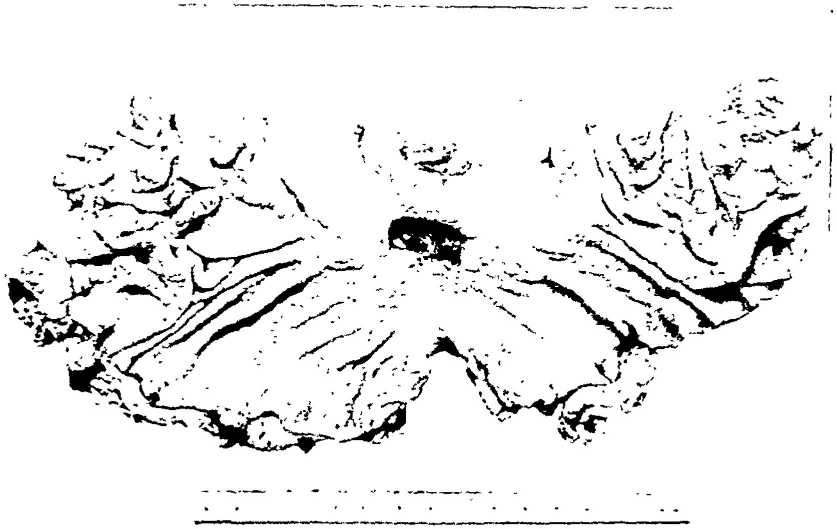


Fig. 3 (case 4).—Resected gastric ulcer. Compare this illustration with figure 1 and with *A* in the colored plate. The gastritic nodules seen gastroscopically can be observed in the gross specimen.

In this case the clinical picture and the gastroscopic picture were in complete agreement. It should be noted, however, that the roentgenologist considered the possibility of a malignant ulcer more likely, whereas the gastroscopic picture definitely showed the ulcer to be benign. Another point of interest is that the ulcer appeared shallower on the second gastroscopic examination, whereas there was no difference in the results of the two roentgen examinations. It cannot be proved, of course, which impression was correct. The microscopic specimen confirmed the gastroscopic findings of severe hypertrophic gastritis around the ulcer.

Because of the fact that so many of the deep ulcers which were observed gastroscopically healed under the medical management of Dr. Palmer and his staff, we are unable to report on a greater number of cases in which operation was performed. In some cases we could follow this healing process through numerous gastroscopies, until complete epithelization took place.

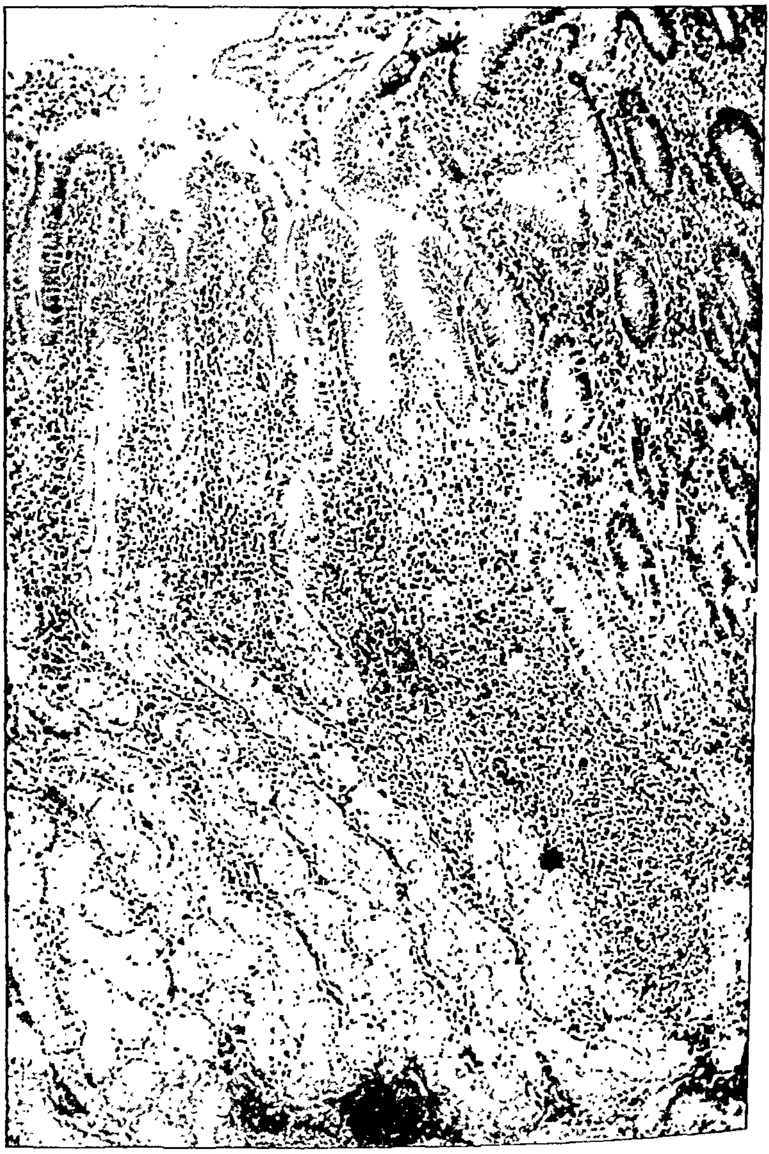


Fig. 4 (case 4).—Photomicrograph of a section made through the gastritic area shown in figure 2. Note the proliferation of the surface epithelium and the tremendous interstitial infiltration without alteration of the long gastric glands.

Carcinomas.—Case 5.—*History.*—The patient, aged 70, from the Cook County Hospital, was referred for gastroscopy by Dr. Harry Singer because of weakness and tarry stools.

Roentgen Examination.—The roentgenogram showed a small pancake-like infiltrative lesion of the prepyloric area with nichelike formation of the lesser curvature. It was uncertain whether the lesion was an ulcer or a carcinoma.

Gastroscopy (April 17, 1935).—Just beneath the angulus a small, jagged prominence was seen during inspiration, the color of which was darker than that of the angulus itself. The mucous membrane of the lesser curvature above the angulus was without marked changes, although we had the impression that it was stiff and infiltrated. In spite of the fact that the involved area was seen only for parts of a second, we were of the opinion that the condition must be a carcinoma of the lesser curvature of the antrum. The size of the tumor could not be estimated.

Operation (June 30).—Resection was done for carcinoma. Microscopic examination of the specimen showed ulcerative adenocarcinoma.

This case illustrates the difficulties of making a diagnosis even with gastroscopy. The lesion was situated in that part of the stomach which is the most difficult to see, i. e., the "blind" area of the lesser curvature of the antrum. A benign ulcer would never have been seen, although in some cases radial folds converging toward the angulus, causing the appearance of a sharp angle instead of the usual parabolic line, may indicate a hidden ulcer. In this case we were fortunate to see part of the lesion, even if for only a part of a second. This indicated with certainty that the lesion was malignant. Nevertheless, it must be admitted that a small carcinoma of this region may be overlooked, although we have never seen such a case.

Case 6.—*History.*—A woman aged 38, seen on Oct. 12, 1934, complained of vomiting for the past two years from once to three times weekly. About three months before the present examination the vomiting increased in frequency, and two weeks before it occurred after almost every meal. The vomitus contained some undigested food and "brown foamy stuff" which tasted bitter. Recently this had been followed by burning pains around the umbilicus. The patient's appetite had been good, but for the past two weeks she had been afraid to take food because of the pain and vomiting which followed. There had been a loss of weight of 22 pounds (10 Kg.) in the last two months, unassociated with loss of strength. The patient was nervous and restless.

Physical Examination.—No abnormalities were found.

Laboratory Examination.—The red cell count was 5,040,000 and the white cell count 7,100. Gastric fluid obtained after an Ewald test meal showed: free acid, 9, and total acid, 106 (questionable). The stools gave a 4 plus reaction to the benzidine test for blood.

Roentgen Examination.—The roentgenogram showed a large penetrating crater on the lesser curvature of the stomach. The mucosal folds about this lesion and on the greater curvature were thickened and stiffened. The patient complained of marked tenderness over this area, and at times it seemed that an indefinite mass could be palpated. We were unable to differentiate definitely between ulcer with associated regional gastritis or ulcer with associated carcinomatous infiltration. The impression was that there was a penetrating ulcer with associated regional gastritis. Carcinomatous infiltration could not be absolutely ruled out. The suggestion was made that the patient be referred for gastroscopy.

Gastroscopy.—A few centimeters above the angulus a large prominence of the lesser curvature was seen. An ulcer of irregular shape, with very irregular edges and surrounded by a definite wall, was found. There was no distinct edge, the ulcerated surface passing gradually into the mucous membrane of the wall, which was swollen and contained pigment spots.

On the basis of the examination it was decided that this was not the picture of a benign ulcer; a malignant lesion of the lesser curvature was suspected.

Operation (October 16).—A large carcinomatous mass was found involving the lesser curvature of the stomach extending almost to the cardia. Practically the entire stomach as well as a large section of the transverse mesocolon was resected. A posterior gastro-enterostomy was done between the first part of the jejunum and the small stump of the remaining portion of the stomach. Recovery was uneventful.

Pathologic Examination.—A crateriform ulcer, 4 by 3.5 by 1.5 cm., was seen. The base of the ulcer extended through much of the wall of the stomach and probably into the adherent omentum. Microscopic examination of a section through the margin of the large ulcerating lesion showed normal mucosa at the fundus which abruptly became necrotic, giving the typical appearance of the crater of an ulcer. Beneath the crater the wall of the stomach was composed of dense edematous fibrous tissue. The entire wall was infiltrated by carcinoma cells, varying greatly in size and appearance and showing areas of "colloidal" transformation with numerous signet ring cells. A section through the wall farthest from the lesion showed no carcinoma but a diffuse infiltration of the muscularis by polymorphonuclears.

In this case, in which the symptoms were of long duration, the roentgen examination could not establish a differential diagnosis between a benign and a malignant lesion. A benign lesion seemed to be more probable; however, the roentgenologist suggested the gastroscopic examination, which definitely proved the malignancy of the lesion. This close cooperation between the roentgenologist and the gastroscopist seems to us to show the proper attitude and the one which is to the best interests of the patient. Each method complements the other; they should most certainly not be regarded as methods of competition. Although in this case the development of a carcinoma from a benign ulcer cannot be proved, it is possible. It is quite certain that an earlier gastroscopic examination would have revealed the beginning carcinomatous formation. This case will again be mentioned in the section concerning operability of carcinomas and the value of early diagnosis in gastric carcinoma.

We consider the following the most important case presented in this paper.

Case 7.—*History.*—A man aged 71, seen on June 4, 1935, three years before suffered from gnawing epigastric distress one or two hours after eating. A [illegible] genogram demonstrated an ulcer, but the patient was not informed whether it was duodenal or gastric. He was placed on a diet, whereupon the distress disappeared. He had no further difficulties until about four months before the present examination, at which time he had daily distress which was relieved by the ingestion of powders or food. There was no loss of weight.

Physical Examination.—Bronchiectasis and obliterative pleuritis of the left side of the chest were found to be present. A roentgenogram of the heart showed the organ to be 29 per cent oversized. No mass could be palpated in the abdomen. and there was no tenderness.

Laboratory Examination.—The histamine test showed free acid (28) after thirty minutes. The stools gave a negative to a 4 plus reaction to the benzidine test for blood.

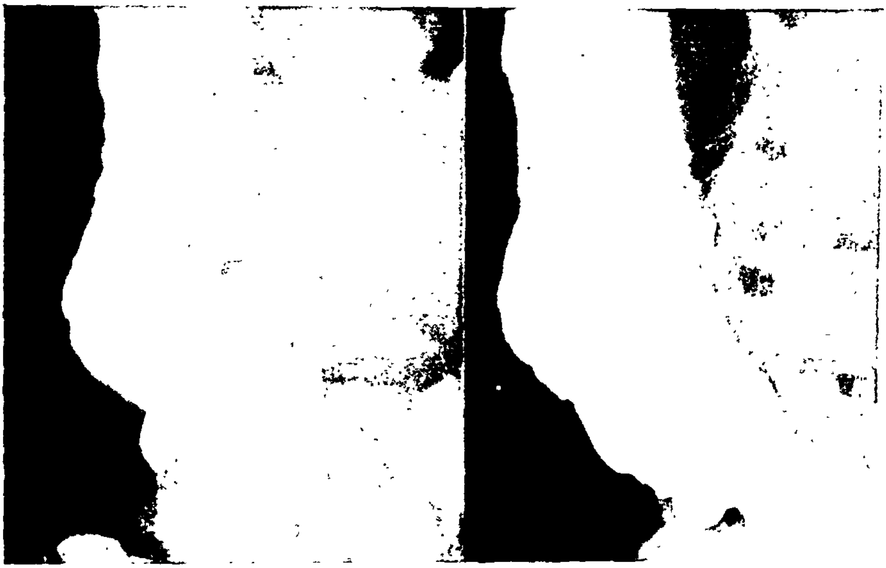

A B

Fig. 5 (case 7).—*A*, roentgenogram made on June 21, 1935. The large niche of the lesser curvature was believed to represent a benign ulcer. *B*, roentgenogram made nineteen days later. The markedly reduced size of the niche seemed to prove definitely the benign nature of the lesion. Compare with *C* and *D* in the color plate, *C* corresponding with figure 5 *A* and *D*, with figure 5 *B*.

Roentgen Examination.—We shall give the results of all examinations in connection with this case. It may be mentioned here that the fifth and sixth readings were proved to be incorrect. They were revised after comparison with the gross specimen.

June 17: A large penetrating ulcer of the cardiac end of the lesser curvature of the stomach was seen.

June 21: A benign penetrating ulcer of the cardiac end of the lesser curvature of the stomach was observed (fig. 5 *A*).

July 9: The crater was smaller (fig. 5 *B*).

July 19: The crater was becoming smaller

August 9: The ulcer of the cardiac end was again becoming larger. A second lesion was present at the lower end of the lesser curvature of the stomach. One or both of the lesions were thought to be neoplastic.

August 26: The penetrating ulcer was still present. The second lesion was present at the lower end of the lesser curvature. The latter was probably carcinomatous.

October 31: There was no second lesion. The large crater was still present at the cardia of the lesser curvature.

First Gastroscopy (June 22).—A sharp picture of the lesser curvature was obtained. There was a large crater-like ulcer, the edge of which was rather sharp, but the whole cavity was filled with blood coagula. In this blood was seen a grayish ridgelike prominence. The mucous membrane surrounding the ulcer was partly thinned and partly swollen. On the basis of the gastroscopic findings a diagnosis of ulcer-like carcinoma of the lesser curvature of the stomach was made. In spite of the high location, the carcinoma seemed to be so well limited that a radical operation was not completely out of the question. (See *C* in the color plate.)

Second Gastroscopy (July 8).—The pyloric region was instantly seen. About the entrance of the antrum the mucous membrane pattern was extremely irregular. On the anterior wall of the greater curvature there were nodes of varying size. On the lesser curvature, just above this point, an elevation was observed, on top of which was an ulcer. The edge of this ulcer lying toward the pylorus was not sharply defined, but all other edges were well demarcated. The floor was grayish white and was not bleeding. The slope of the elevation was extremely reddened and appeared to be edematous. The nodular changes at the entrance of the antrum were too large to permit a diagnosis of nodular gastritis. Carcinomatous infiltration was suspected. Furthermore, the ulcer of the lesser curvature did not have the appearance of the usual benign ulcer because of its situation on an elevated area and because one part of its edge was not sharply defined. For these reasons we believed that a carcinomatous lesion was present which was well limited toward the cardiac portion of the stomach but appeared to be progressive toward the pyloric part. Radical operation seemed to be possible at this stage. (See *D* in the color plate.)

Operation (November 4).—An ulcerating lesion was felt in the lesser curvature upward toward the cardia. About seven eighths of the stomach was resected. The patient died on November 8 from bronchopneumonia. Permission for autopsy was not given.

Pathologic Examination.—Carcinoma was found on the lesser curvature. Microscopic examination showed colloidal carcinoma of the mucosa, well defined against the muscularis mucosae but invading the lymph vessels of the submucosa. The distant parts of the wall of the stomach showed dilatation of blood vessels and edema of the submucosa, which was three times thicker than usual (figs. 6 and 7).

This case demonstrates the superiority of gastroscopy over all other methods in arriving at this diagnosis. The history, and particularly the roentgenogram, suggested a benign lesion. Even after knowing of the presence of carcinoma, as proved microscopically, no one could find the least evidence of it either in or hidden by the mucosal folds, which the roentgenogram showed to be radiating from the ulcer. The pathologic examination offers the explanation: The carcinoma was almost noninvading. It did not even invade the muscularis mucosae. The gastroscopic picture, however, was definite, even after the first examination, at which the crater of the ulcer was seen filled with blood. It must be pointed out

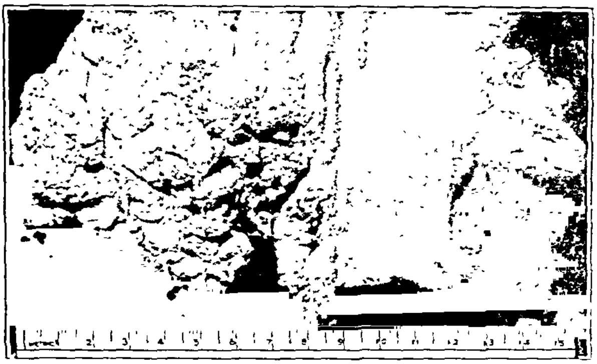


Fig. 6 (case 7).—Gross specimen of a carcinoma of the lesser curvature of the stomach after resection. Compare with *C* and *D* in the color plate. The resection was made four months after the second gastroscopy.

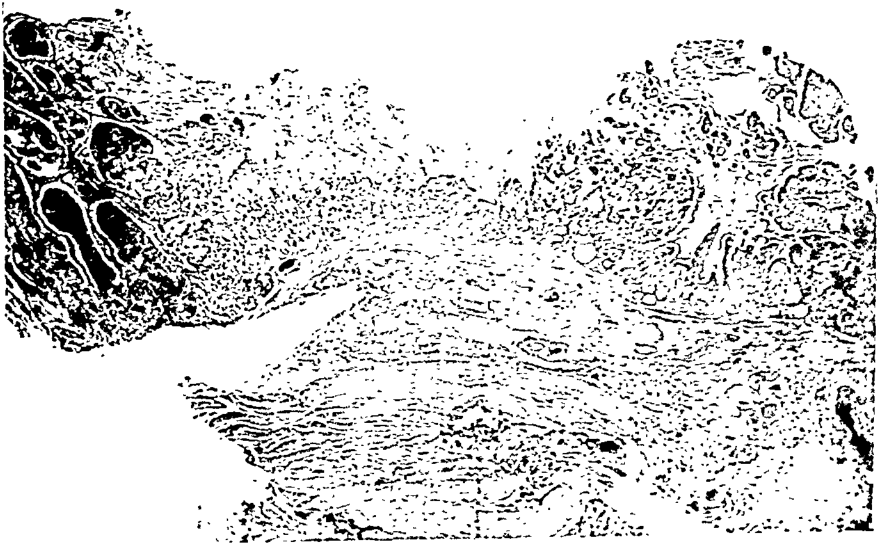


Fig. 7 (case 7).—Photomicrograph of a section made through the carcinoma shown in figure 6. Compare with *C* and *D* in the color plate. A colloid carcinoma of the mucosa is well defined against the muscularis mucosa but is invading the lymph vessels of the submucosa.

that much experience is necessary for such endoscopic accuracy; this is naturally also true of other diagnostic procedures. Here again it is possible, but it cannot be proved, that the carcinoma developed from a preceding ulcer. The gastroscopic findings were so exact that even the enlargement of the mucosal blood vessels were seen (redness of the wall), and the edema of the gastric wall was described. The patient was not anxious to have an operation, and because he was a poor operative risk he was not urged too strongly. The fact that the niche in the roentgenogram became shallower during the observation while the carcinoma was progressive seemed to us to be important. Such cases have been described by Bloomfield.[3] It is obviously dangerous to assume that a niche is produced by a benign ulcer because it becomes shallower during roentgen observation of a few weeks; early gastroscopy is indispensable. We shall later discuss the fact that here a true "early" diagnosis of a gastric carcinoma was made by means of gastroscopy.

Conclusions.—Operation was performed on seven patients, in each of whom it was not quite certain clinically whether a benign or a malignant ulceration of the stomach was present. In four of these cases the ulcer was proved microscopically to be benign; in all of these cases the roentgen examination gave doubtful results, and in two carcinoma was thought to have been present. Gastroscopy established a correct diagnosis in every instance.

In three of the original cases the lesion was proved to be carcinomatous. The roentgen diagnosis was incorrect in one instance and uncertain in the remaining two. The gastroscopic diagnosis again was correct in each case. The case in which a malignant ulcer was diagnosed gastroscopically but in which the ulcer was thought to be benign, both by clinical impression and by the fact that the lesion became shallower on repeated roentgen examinations, will be discussed later. The splendid cooperation between the roentgenologist and the gastroscopist was appreciated as being of great value.

OPERABILITY OF CARCINOMA AS DETERMINED BY GASTROSCOPY

Inoperable Tumors.—The inoperability of a tumor is dependent not only on the local gastric findings but also on the general condition of the patient and on the presence or absence of metastases. Nevertheless, the inoperability may become evident instantly by gastroscopy. It may be shown that the tumor is not sharply defined and that the infiltration extends too high to allow even a radical operation. This can usually be demonstrated better by gastroscopy than by roentgen examination. We believe that no surgeon considers the exploratory operation satisfactory in cases in which the condition proves to be inoperable. Bier has said that exploratory laparotomy in cases of gastric cancer is murderous. We believe, however, that before the introduction of gastroscopy exploration was warranted in many cases but that now it should seldom be necessary after careful examination by a well trained gastroscopist.

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[3] Bloomfield, A. L.: Diagnosis of Early Cancerous Changes in Peptic Ulcer, J. A. M. A. **104**:1197-1201 (April 6) 1935.

CASE 8.—*History.*—A man aged 64, seen on March 6, 1935, suffered from epigastric pain for ten weeks.

Physical Examination.—A hard movable mass was found in the left upper quadrant of the abdomen.

Laboratory Examination.—The gastric contents showed: free acid, 0. and total acid, 15.

Roentgen Examination (March 11).—A large gastric carcinoma, probably of the medullary type and probably located on the posterior wall, was thought to be present. The lesion extended high along the greater curvature, possibly so high as to be inoperable.

Gastroscopy (March 8).—The nodular angulus was overhanging the entrance of the antrum so that only a small portion of the antrum could be seen. The angulus and the lesser curvature above the angulus were stiff and infiltrated and showed numerous nodules. Color changes were present. The same findings were seen in the posterior wall, and, to a less extent, in the lesser curvature. There was no sharp limit of the mucous membrane, but we had the impression that from about 8 cm. beyond the cardia the mucous membrane was rather normal. On the basis of the gastroscopic findings a diagnosis of infiltrating cancer without sharp limits was made. In spite of the fact that the cancer was situated rather low in the stomach, its limits were not sharp, and because of this we believed that the chances of a successful operation were poor.

Operation.—A huge carcinoma was found involving the distal two thirds of the stomach. There were metastases along both the greater and the lesser curvature. The condition was considered inoperable. The patient died on March 18 of pulmonary embolism.

Autopsy.—Ulcerating carcinoma of the prepyloric area of the stomach was found arising in the posterior wall and permeating the wall of the stomach; it extended radially to the perigastric, pancreatic and periaortic lymph nodes from the level of the cardia to that of the renal vein, etc. Microscopic examination showed that the carcinoma had arisen in the gastric mucosa; it had spread through the lymphatics and permeated the wall of the stomach. The neoplasm consisted of atypical hyperchromatic epithelial cells which were growing in masses but with a definite tendency to tubule formation in places. The lymphatic spaces in the serosa of the stomach were dilated and filled with masses of carcinoma cells.

The carcinoma was considered inoperable because of both roentgen and gastroscopic observations; the latter showed infiltration and lack of sharp limitation of the lesion. Later the microscopic examination showed the diffuse infiltration of the wall of the stomach and the invasion of the lymphatic spaces of the serosa. Operation was attempted; the patient died from embolism.

CASE 9.—*History.*—A man aged 63, seen on Jan. 7, 1935, suffered from abdominal distress for eight months, with belching and regurgitation. There had been loss of appetite and weakness of about one year's duration.

Physical Examination.—An epigastric mass, unmovable and about 4 cm. in diameter, was felt.

Roentgen Examination (January 8).—The picture was that of polypoid carcinoma involving the central portion of the stomach. The extreme cardiac end and the pylorus were believed to be free from infiltration.

Gastroscopy (January 9).—A hard mass was felt a few centimeters below the cardia on the passage of the Ewald tube. The gastroscope could be introduced just beyond the cardia. In the lesser curvature a hemorrhagic infiltration was seen. The diagnosis was a large neoplasm of the upper part of the stomach, infiltrating the lesser curvature.

Operation (November 2).—A large thickened mass involving most of the greater curvature and most of the posterior wall and extending from the lower third to within about 2 cm. of the cardiac orifice was found. It was decided that an attempt at subtotal gastrectomy could not be successful since the stomach was adherent to the carcinoma, which had grown beyond the confines of the stomach. High voltage roentgen therapy improved the condition.

There was general agreement concerning the nature of the lesion. The carcinoma extended almost up to the cardia. The inoperability was best shown by gastroscopy. Such infiltrating lesions without sharp demarcation in the upper part of the stomach must always be considered as being unfavorable for operation, especially if the gastroscope cannot be completely introduced. It is questionable whether gastroscopy was not contraindicated in this case. Our diagnosis of infiltration of the lesser curvature of the stomach was shown to be incorrect. This case, with others, has influenced our new conception of gastroscopic orientation in the upper parts of the stomach.

Case 10.—*History.*—A patient aged 50, seen on April 24, 1935, suffered from weakness and a constant dull aching pain in the epigastrium for two months. He had lost 30 pounds (13.6 Kg.) in weight since Jan. 1, 1935.

Physical Examination.—No abnormalities were found.

Laboratory Examination.—The gastric fluid after the injection of histamine showed no free acid. The stools gave a 4 plus reaction to the benzidine test for blood. The blood showed 60 per cent hemoglobin and 4,000,000 red blood cells.

Roentgen Examination (April 26).—The roentgenogram showed a large carcinoma situated high on the lesser curvature of the stomach with a ragged crater at the center.

Gastroscopy (April 27).—At the cardia marked resistance was felt, but it was possible to bring the instrument into the stomach. Instantly a large tumor was seen on the anterior wall invading the lesser curvature. It extended from about the region of the angulus up to the cardia. The bleeding protrusion was not sharply limited and contained an irregular yellowish white ulceration. A diagnosis of a large carcinoma of the anterior wall and lesser curvature, not sharply limited, involving the cardia, was made. In our opinion the condition was inoperable but probably suitable for roentgen therapy.

Operation (April 30).—The stomach was examined and found to be involved by a carcinoma which extended along the lesser curvature, reaching up to the esophagus and infiltrating the grastrohepatic mesentery. Metastases were found in the liver. The involved portion of the stomach was fixed to the posterior parietes so that it could not be brought down and lifted out into the field. The patient was discharged on May 27 and died on July 3.

Roentgen examination and gastroscopy showed a carcinoma situated high up on the lesser curvature of the stomach. Gastroscopy gave evidence of its inoperability.

A 75 year old man had epigastric distress for one year, which was relieved by food. Physical examination gave essentially negative results except for a slight enlargement of the heart accompanied by an apical systolic murmur. The gastric fluid showed no free acid. The stools gave a 4 plus reaction to the benzidine test for blood. Roentgen examination revealed a penetrating ulcer of the lesser curvature of the stomach with infiltration of the lesser curvature (fig. 8). The roentgenologist felt that the extreme cardiac end of the stomach was not involved, but the examination was difficult because of the inability of the patient to relax. The gastroscopic findings follow: The pylorus and the antrum were about normal. Just above the angulus a grayish white tumor appeared involving the lesser curvature, the anterior wall and the greater curvature. Protruding nodes were seen on the lesser curvature only. In other parts there were a whitish infiltration and rigidity of the entire mucous membrane. This picture was seen just below the cardia, although even the cardia was somewhat infiltrated; its mucous membrane was bleeding, and during the introduction of the instrument a slight resistance was felt at this point. A week later, as the chief of the gastro-enterologic department wanted to see the picture, gastroscopy was repeated. In this short time the changes had increased considerably, and the cardia was definitely involved; an ulceration was also seen. Dr. Palmer decided against a laparotomy after being shown these findings. In this case, again, gastroscopy showed much more detail than the roentgenogram. (See *B* in the color plate.)

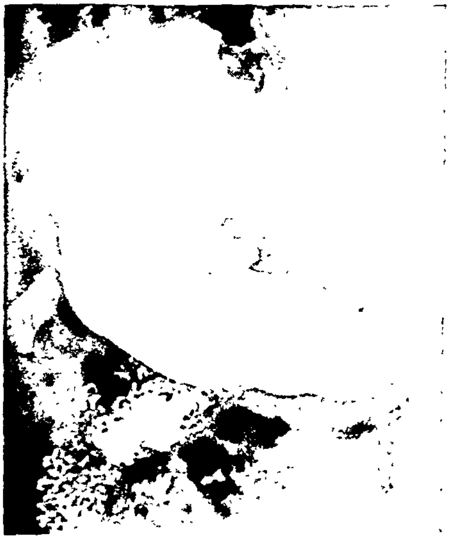

Fig. 8.—Roentgenogram in a case in which operation was not performed because gastroscopy (see *B* in the color plate) definitely proved the inoperability of the growth.

Operable Tumors.—In this discussion we shall briefly refer to cases 5, 6 and 7 and present three others. In case 5 operability was shown after gastroscopic examination by the fact that the tumor was seen only on the angulus. Operability was deemed likely in case 6, but we could not be certain since the gastroscopic picture showed the edge of the ulcer passing into the normal mucous membrane. However, it could not be said that operation was out of the question. Practically the entire stomach and a large section of the transverse mesocolon were resected. Certainly the gastroscopic picture gave a more correct impression of the seriousness of the case than did the roentgen examination. In case 7, we stated, after gastroscopy, a half-year before the operation, that the tumor would be operable. If the patient had been convinced of the necessity of the operation earlier he might have survived, since the lesion was relatively benign and well confined. This case illustrates the obvious fact that an early diagnosis is of little value if the patient will not cooperate.

Case 11.—*History.*—A man aged 63, seen on Aug. 1, 1934, for the past twenty-five years had epigastric distress consisting of a localized burning pain occurring two or three hours after meal time and at about 2 a. m. This distress was always relieved by the ingestion of food. On two occasions his condition was diagnosed as a gastric ulcer. Since June 1933 his distress had changed somewhat. He complained of dull epigastric pain associated with fulness immediately after eating. His appetite had been poor, and he had lost 15 pounds (6.8 Kg.) in weight.

Physical Examination.—A questionable mass was felt in the epigastrium; otherwise the results of the examination were negative.

Laboratory Examination.—The gastric fluid obtained after an Ewald test meal showed: free acid, 29, and total acid, 75. The stools gave a 4 plus reaction to the benzidine test for blood.

Roentgen Examination.—The picture was that of carcinoma of the stomach with partial obstruction. The upper two thirds of the lesser curvature appeared pliable and did not appear to be infiltrated. The lower three fourths of the greater curvature also appeared to be pliable, with no infiltration. The patient would not give permission for operation. He was readmitted to the hospital on December 21.

Clinical Impression.—On the basis of the clinical picture the condition was thought to be a large carcinoma of the stomach, probably inoperable, but with no demonstrable metastases.

Gastroscopy (December 24).—The pylorus was instantly seen. It was a small, completely rigid hole, the posterior wall of which was covered by a prominent round tumor on which were seen two nodes. The border was well marked except for the posterior side, where no real edge could be seen. At this point there seemed to be a diffuse infiltration of the posterior wall where the mucous membrane was very thin, and a large blood vessel could be observed. The upper portions of the posterior wall, however, were quite normal, as were all the other portions of the mucous membrane except for being somewhat more pale than usual. The distal node of the tumor showed a pink and spotted mucous membrane; it covered the pyloric channel, behind which an ulceration might possibly have been found. The proximal node was darker, and a large hemorrhage was seen in its mucous membrane. A diagnosis was made of carcinoma of the posterior wall of the antric channel infiltrating the lower posterior wall of the body of the stomach; nevertheless, it was thought that a radical operation could well be attempted because the tumor did not reach the upper parts of the stomach.

Operation (December 26).—The stomach was easily movable and could be brought up out of the abdomen. The carcinoma involved the entire circumference of the stomach close to the pylorus and had invaded the transverse mesocolon. Gastrectomy was done. The patient died of pneumonia on the second day after operation.

Pathologic Examination.—There was an ulcer crater measuring 4.8 by 3.3 by 0.8 cm., with sharp soft edges. It rested on fibrous tissue in which were found small nests of carcinoma cells. The wall adjacent to the ulcer was densely infiltrated with carcinoma cells arranged in long thin cords. A section through the wall of the stomach some distance from the carcinoma did not contain carcinoma cells but showed definite polymorphonuclear infiltration about the vessels of the anterior coat of muscle.

Autopsy.—No metastases were found.

The symptoms of long duration (twenty-five years) indicate that either an ulcer or chronic gastritis preceded the carcinoma. The clinical impression was that the condition was an inoperable carcinoma; the roentgenogram indicated that the tumor was movable; gastroscopy pointed out that a resection would be possible. The two last-mentioned impressions were found to be correct.

Case 12.—*History.*—A 41 year old woman, seen on Nov. 13, 1934, suffered from pain in the lower half of the abdomen for two years, gnawing abdominal pain for the past eight months when the stomach was full and nausea and vomiting for the past three months.

Physical Examination.—A firm fixed mass was found in the abdomen which was painful on deep palpation. It was about 8 by 10 cm. in diameter and extended about 1½ inches (3.8 cm.) below the umbilicus.

Laboratory Examination.—The gastric fluid obtained after an Ewald test meal showed: free acid, from 28 to 60; total acid, from 40 to 70 and sarcinas. The stool gave a 3 plus reaction to the benzidine test for blood on one occasion.

First Gastroscopy (November 16).—On the greater curvature of the antrum just at the pylorus was seen a large ulcer with a dark brown floor and irregular edges, which were surrounded by an elevated reddened wall which seemed to be infiltrated but contained no nodules. Peristaltic waves were seen on the side of the lesser curvature passing toward the pylorus. The upper parts of the mucous membrane were normal except for one small area high on the posterior wall, where some edema was seen, in the middle of which was found a small but definite dimple-like ulcer with elevated edges and a brownish floor. On the basis of the gastroscopic findings a diagnosis was made of cancer of the pylorus and the greater curvature, which was sharply limited (which probably could be radically resected), and circumscript hypertrophic gastritis of the upper posterior wall with a small ulceration, which was probably metastasis to the mucous membrane.

Roentgen Examination (November 16).—The roentgen picture was that of annular carcinoma of the antrum of the stomach. An inflammatory lesion with massive adhesions about the stomach could not be ruled out, but the possibility of such a diagnosis was doubtful.

Operation (November 17).—Carcinoma was found in a movable stomach. The pyloric region was involved, the glands along the pancreas were enlarged and one small metastasis was found at the site of the gallbladder. Since resection was easy, it was done in preference to gastro-enterostomy because of the greater palliative relief. About half of the stomach was resected.

Pathologic Examination.—A large ulcerous crater was seen lying in carcinomatous tissue with irregular, firm borders and measuring 4 by 1.5 cm. Microscopic examination showed normal mucosa along one border, which abruptly ran into the superficially necrotic ulcer bed. Beneath the normal mucosa and the ulceration, the normal structures were replaced by large irregular areas of typical small groups of carcinoma cells containing colloid and being of the signet ring type. High voltage roentgen therapy was followed by recovery.

Second Gastroscopy (December 20).—Most severe inflammation of the whole mucous membrane was seen, certainly due to the roentgen treatment. Metastases could not be seen.

Roentgen examination revealed the carcinoma in this case; there were some doubts concerning the lesion, however. Gastroscopy showed the carcinoma with the greatest certainty; it further indicated the advisability of resection because of the sharp limits of the tumor. The presence of metastases as a probability was also mentioned. All these observations were confirmed by operation.

Case 13.—*History.*—A 50 year old man, seen on Aug. 2, 1935, had suffered from gaseous distention and loss of weight for the past eight months.

Physical Examination.—Resistance was encountered in the epigastrium, and a systolic murmur was heard.

Laboratory Examination.—The stools were repeatedly normal.

Gastroscopy (August 5).—Some food remnants were present in the contents of the stomach obtained during fasting. There was an irregular, central, elevated, granular wall which was slightly more red than usual, even having a brownish tinge, and in the middle of which was seen a dark crater. The surrounding mucous membrane showed no significant changes; the upper parts of the stomach were normal. A diagnosis was made of circular carcinoma of the pylorus, well limited. It was thought likely that a radical operation could be performed successfully. (The growth was so typical of an operable carcinoma that we present here a reproduction of the gastroscopic picture [*E* in the color plate], together with a photograph of the gross and microscopic specimens.)

Roentgen Examination (August 5).—The roentgen picture was that of neoplastic involvement of the prepyloric portion of the stomach by a constricting and apparently polypoid type of tumor.

Operation (August 5).—The pyloric region was found to be involved by a hard tumor mass the size of a walnut. Several hard lymph nodes were present at the lesser and greater curvatures. Subtotal gastrectomy was done (because of the lymph nodes). The patient died from postoperative hemorrhage.

Pathologic Examination.—The gross specimen presented almost the exact picture that was seen by gastroscopy. Microscopic examination showed the cell the mucosa to be atypical, being arranged in cords, with alveoli deeply infiltrating the wall of the stomach. There was no tumor in the cardiac end. The lymph nodes showed evidence of carcinoma (figs. 9 and 10).

Subtotal gastrectomy was done because of the presence of the involved lypmh nodes. The neoplasm was as sharply limited as gastroscopy had shown it to be. It is probable that there was no carcinomatous invasion of the lymph nodes a few months earlier, and if the patient had been seen at that time his life might have been saved. This illustrates the great importance of early gastroscopic examination, since the malignant nature of even very early lesions can thus be established.

Conclusions.—Nine cases of gastric carcinoma were observed in which the question of operability arose. In three of these cases the condition was found at operation to be inoperable. In two of them roentgen examination and gastroscopy were in agreement concerning the impossibility of a radical operation. The condition in the remaining case was also found to be inoperable by gastroscopy; the roengenographic protocol gave no opinion concerning this point.

A radical operation was performed in the remaining six cases; in three the condition was found to be definitely operable after gastroscopic examination. Not only was this true, but the findings at operation were almost identical with those described in the gastroscopic protocols. The final three cases presented complete agreement in only one instance between the roentgen examination and the gastroscopic examination: here both methods demonstrated the operability of the lesion. The fifth lesion was shown by the roentgenogram to be operable, whereas the gastroscopist stated that though the original growth was definitely operable he believed metastases to have taken place. This was found to be true. In the remaining case differentiation between a benign and a malignant ulcer could not be made roentgenographically. Gastroscopy answered this question, and, moreover, the results of operation were considered doubtful. This was borne out by the finding of metastatic lymph nodes, which necessitated subtotal gastrectomy.

VALUE OF GASTROSCOPY IN THE "EARLY" DIAGNOSIS OF GASTRIC CARCINOMA [4]

We shall consider an "early" diagnosis of carcinoma of the stomach as being one which makes it possible to bring about a cure of from three to five years' duration. Although operation must be considered the only method of cure, high voltage roentgen therapy by the Coutard method may be tried in cases in which the lesion is inoperable. Curiously. general practitioners, and even gastro-enterologists, are found who do

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[4] Refer to cases 7 and 29. A more extensive discussion of this question will be found in the senior author's book on "Gastroscopy" (Chicago, University of Chicago Press, 1937), which contains ninety-six colored pictures of gastroscopic findings.

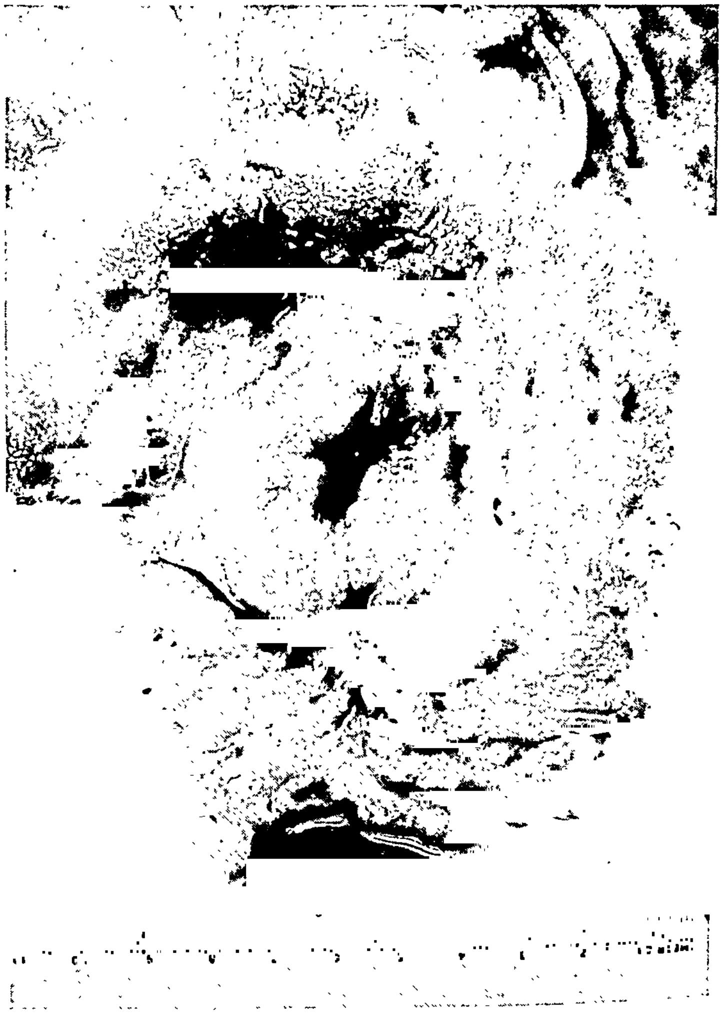

Fig. 9 (case 13).—Resected gross specimen of the carcinoma. Compare with *E* in color plate. The growth is a typical sharply limited operable carcinoma.

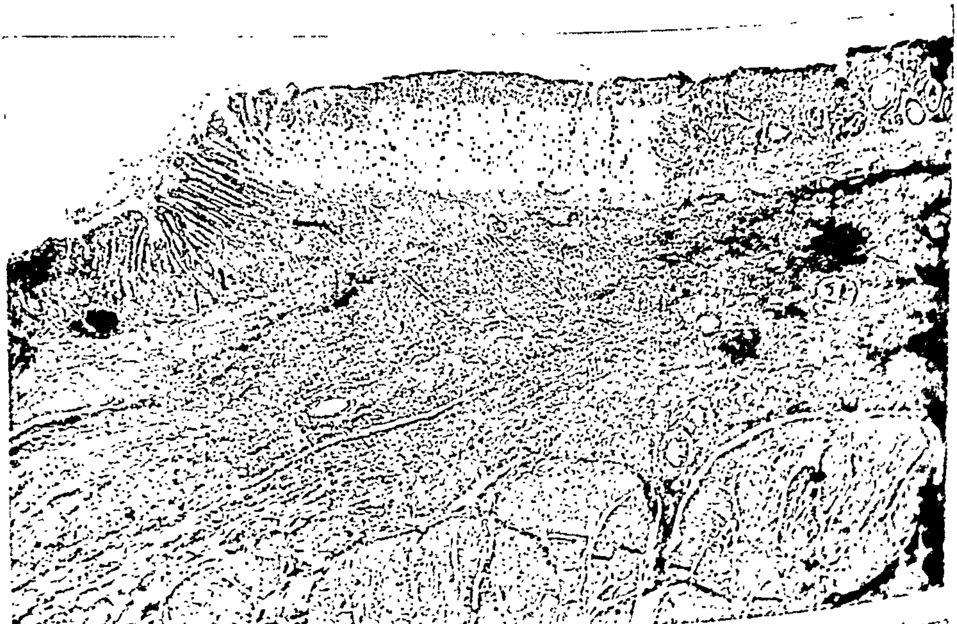

Fig. 10 (case 13).—Photomicrograph of a section made through the carcinoma shown in figure 9. Note the sharp demarcation between the tumor (at the right) and the normal gastric glands (at the left).

not believe that good results are often obtained from gastric resection in cases of carcinoma of the stomach. One of us[5] has followed three patients for over ten years after this operation. Only one of them is known to have died, death resulting from a recurrence eleven years later. Numerous cases were observed in Munich in which the operation resulted in complete cure for from three to five years. Recent German statistics concerning the success of gastric resection in cases of carcinoma give a surprisingly high percentage of cures; it is unfortunate that the records are not available to us. This success was obtained because the cases were well chosen.

We believe that exploratory laparotomy is responsible, to a great measure, for the attitude common among the laymen and many medical men that in general operation for cancer of the stomach is hopeless. This attitude is not so difficult to understand. These persons are cognizant of the fact that even though operation has been attempted, in cases of advanced gastric carcinoma the ultimate prognosis is seldom better than before, and they believe this result obtains after surgical intervention in all cases of carcinoma of the stomach. It is our contention that if exploratory laparotomy could be done away with, except in those relatively few cases in which gastroscopy does not settle the question definitely, the mortality would be decreased to the point where patients would be willing to undergo operation. They would learn that early cancer can be cured by this procedure, whereas it is not even attempted on late cancer. In short, they may be brought to realize that the prognosis of early cancer is a different thing from the prognosis of late cancer. This would result, in our opinion, not only in more operations in cases of gastric carcinoma, but particularly in a higher percentage of operations in cases of the early stage in which definite cure is most likely to be brought about.

Boas said that by the time symptoms are present it is almost invariably too late to bring about a cure in cases of gastric carcinoma. This statement, frequently repeated, is not correct. If we control the few cases cited here we find histories of distress for periods of ten weeks, five months, eight months (two cases), two years (two cases) and twenty-five years (one case). In this last case it was probable that a benign ulcer was first present and that the carcinoma developed within the past six months. It is true that there are cases in which the lesion is inoperable fourteen days after the first symptom is noticed, but they are not frequent. Often early symptoms are present, or a history of symptoms of long standing (ulcer, atrophic gastritis, benign tumor) precedes the beginning of the carcinoma. Also, we must admit that there are types of carcinoma for which the prognosis is bad even with early diagnosis and operation. This is illustrated by the type which diffusely infiltrates the body of the stomach. The sharply limited tumors, even though they are of upper parts of the stomach, give good surgical results if the operation is done before the lymph nodes have been involved.

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[5] Schindler, R.: Die Bedeutung der Gastroskopie für die Heilung des Magenkrebses, Monatschr. f Krebsbekämpf. **1**:203-208 (May) 1933.

In order to improve the results of operation for gastric carcinoma and in order to dissipate the unjustified distrust which patients and even physicians feel regarding this procedure, we offer the following three suggestions:

(*a*) Patients over 35 years of age who have anorexia and loss of weight should be examined roentgenographically and gastroscopically, since it is at this stage of a carcinoma that the best surgical results are to be had. Of course, patients of this age having frank gastric symptoms which are not completely relieved after fourteen days of medical treatment should also be given a thorough examination, including the taking of roentgenograms of the gastro-intestinal tract and gastroscopy.

(*b*) All patients suffering from a gastric carcinoma which is not diffusely infiltrating but is sharply limited should be advised to undergo operation regardless of the location of the neoplasm, unless it is at the extreme cardiac end. On the other hand, a diffusely infiltrating tumor should be operated on only if it is small and if it is strictly confined to the pyloric region.

(*c*) Exploratory laparotomy should be done only in the relatively few cases in which gastroscopy cannot definitely decide the operability of the lesion.

Considering the first suggestion, we might ask what constitutes a "thorough" examination of the stomach. Certainly analyses of the gastric fluid and stools are not sufficient; in the small well limited tumor free acid is often found but occult blood is seldom seen. There are, then, only two methods of great value in this respect: roentgenography and gastroscopy. It is worth while to consider which gives the more valuable information concerning gastric carcinoma. If case 7 is analyzed it is seen that at least in that instance gastroscopy was much superior. This was a true case of "early" diagnosis; the carcinoma was recognized when it was extremely small. The roentgenogram demonstrated the niche but failed to demonstrate its malignant character. (This error was frequently seen in the material from Munich.) Roentgenography is able to indicate the malignant character of an ulcerative lesion if some infiltration has occurred around the lesion, and even then it is difficult to differentiate between inflammatory reaction and neoplastic infiltration. Gastroscopy, however, demonstrates the malignant nature definitely to the trained gastroscopist. Moreover, in polypoid types of tumors gastroscopy can show the malignant development at its inception, while this is often impossible by roentgenography. One of us had the occasion to perform gastroscopy on a patient in Bergmann's Clinic (*charité*) in Berlin whose roentgenograms were suggestive of a benign tumor of the greater curvature; gastroscopy revealed a malignant, decaying, sharply limited carcinoma.

Roentgenographic examination, on the other hand, should theoretically be superior to gastroscopy in some cases since there are certain portions of the stomach "blind spots" which cannot be seen by the latter method. These regions of the stomach which can sometimes not be seen are the lesser curvature of the antrum and a small strip of the posterior wall on which the instrument lies. A small beginning carcinoma should be seen there in some instances when the gastroscope fails to demonstrate the lesion. (Although this is theoretically true, it is interesting to note that Schindler has not seen an instance of this although he has had occasion to observe twenty-four hundred gastroscopies and about six thousand roentgenograms.) Small diffuse carcinomas are difficult to demonstrate by either method; these growths, however, are usually so malignant that even early diagnosis is not of great value in prolonging life.

Conclusions.—The physician and the patient should be convinced of the value of operation for gastric carcinoma. To accomplish this, we suggest that exploratory laparotomy be done only in those few cases in which gastroscopic examination does not definitely settle the question of operability.

Surgical intervention can be done at an early stage if an early diagnosis is made; this, we believe, can be brought about by having every patient over 35 years of age examined both by gastroscopy and by roentgenography if he has been suffering from anorexia, abdominal distress and suggestive loss of weight. We further believe that such patients should be followed and examined gastroscopically and roentgenographically at least twice a year, since there is unanimity of opinion (Konjetzny,[6] Hurst,[7] Henning,[8] Moutier and others) that atrophic gastritis and benign tumor may develop into carcinoma.

No gastric ulcer should be treated without a preceding gastroscopic examination, and this examination should be repeated in those cases in which there is a change in the type of distress, even if the niche as seen in the roentgenogram has become shallower, since this observation does not exclude the possibility of malignancy (see case 7, and compare with Bloomfield's case [3]).

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[6] Konjetzny, G. E.: Ueber die Beziehungen der chronischen Gastritis mit ihren Folgeerscheinungen und des chronischen Magenulcus zur Entwicklung des Magenkrebses, Beitr. z. klin. Chir. **85**:455-519, 1913.

[7] Hurst, A. F.: Alvarez Lecture on Unity of Gastric Disorders, Brit. M. J. **2**:89-94 (July 15) 1933.

[8] Henning, N.: Die Entzündung des Magens, Leipzig, Johann Ambrosius Barth, 1934.

By following this program we can hope to improve the results of operation on gastric neoplasms. This will result in increased confidence of physicians and patients in surgical intervention and will make it possible to bring not only a larger number of patients to the operating table but particularly a higher percentage of patients with early lesions. We may hope in this way greatly to improve the prognosis of the most frequent carcinoma seen in man.

GASTROSCOPY OF THE POSTOPERATIVE STOMACH

There are four principal morphologic changes which may cause trouble (pains, hemorrhages and belching) after gastro-enterostomy or gastric resection. They may be listed as follows:

1. Recurrent or gastrojejunal ulcer. This condition was long thought to be the only complication in the postoperative stomach.

2. Chronic gastritis. The frequency of this postoperative condition was first noted by one of us (R. S.) in 1922; it was then confirmed by all recognized gastroscopists (Korbsch,[9] Hohlweg,[10] Gutzeit, Hübner,[11] Hertel and Kallius,[12] Henning and others) and later by roentgenologists and finally by outstanding surgeons.[13]

3. Erosions and irritation caused by silk sutures remaining from operation, which have cut through the mucous membrane. The importance of this condition was also first noted by one of us [14] and was later confirmed by Henning and Moutier.

4. Carcinoma which develops at the stoma. This condition is rare but has been described; we have observed only two cases gastroscopically.

In our gastroscopic material we present thirty cases in which postoperative examination was made. In seven of these reoperation was done after gastroscopy, thus giving us a biopsic control. We shall first present this group. The remaining twenty-one cases shall be presented briefly, since we have no objective evidence of the accuracy of the gastroscopic findings.

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[9] Korbsch, R.: Zur Kenntnis der chronischen Gastritis, Med. Klin. **21**:959-962 (June 26) 1925.

[10] Hohlweg, H.: Beobachtungen und Betrachtungen auf Grund von 100 Gastroskopien, München. med. Wchnschr. **71**:506-508 (April 18) 1924.

[11] Hübner, A.: Gastroskopie, Ergebn. d. Chir. u. Orthop. **20**:266, 1927.

[12] Hertel, E., and Kallius, H. U.: Beiträge zur Gastroscopie des operierten Magens, Arch. f. klin. Chir. **151**:578-594, 1928.

[13] Clairmont, P.: Die Gastritis nach Magenoperationen, München. med. Wchnschr. **73**:1906 (Nov. 5) 1926.

[14] Schindler, R.: Die diagnostische Bedeutung der Gastroskopie. München. med. Wchnschr. **69**:535-537 (April 14) 1922.

POSTOPERATIVE STOMACH WITH BIOPSIC CONTROL

CASE 14.—*History.*—A 37 year old man, seen on Nov. 16, 1934, in 1924 had had an operation for gastric ulcer. In 1933 he began to complain of pain in the lower abdominal quadrants. The second operation, done on November 24, revealed a jejunal ulcer. Resection of the respective parts of the stomach and the jejunum was done, and a lateral anastomosis was made between the large opening of the stomach and a portion of the jejunum about 5 inches (12.7 cm.) below the old opening. After this, the patient again complained of abdominal pain.

Physical Examination.—The liver was enlarged, but there were no other significant findings.

Laboratory Examination.—Gastric analysis after the injection of histamine showed free acid up to 90. The stools gave a negative to a 3 plus reaction to the benzidine test for blood.

Roentgen Examination (Jan. 18, 1935).—The gastro-enterostomy stoma functioned well. At times a fleck was seen, about 5 or 6 mm. in diameter, near or in the stoma, which seemed to be definite, constant and circumscribed. It must be admitted, however, that its exact nature was not definite, i. e., it was not known whether it was barium in the crater of an ulcer or a bead of barium in the gastro-enterostomy stoma. There was little tenderness over it.

Gastroscopy (January 22).—The antrum was easily seen; cross-folds were running over its greater curvature. The gastro-enterostomy stoma was found lying in the posterior wall. It was a rather round hole from which some grayish fluid passed into the stomach during the patient's respirations. No peristalsis was seen, either of the opening or of the intestine. On the edge of the stoma toward the pylorus there was a deep crater-like ulcer the diameter of which was larger than that of the artificial opening. Its edges were sharp, and its floor was yellowish but somewhat spotted. That part of the ulcer which lay on the side of the anterior wall of the stomach was undermined and made a shadow on the floor of the ulcer. On the opposite side a black silk thread was seen which was hanging from the posterior wall of the gastro-enterostomy stoma. The folds on the cardiac side of the stoma were reddened and somewhat swollen; beyond this the mucous membrane as well as all the other parts of the stomach were normal. The diagnosis on the basis of the gastroscopic findings was a large marginal ulcer at the pyloric side of the posterior gastro-enterostomy stoma and slight gastritis of a small area surrounding the stoma. The silk thread near the stoma had cut through the mucous membrane. (See *F* in the color plate.)

Operation (January 28).—A large penetrating ulcer was found in the jejunum about 1 cm. from the suture line. The junction of the jejunum and the stomach was completely excised. A new side to side anastomosis of the jejunum was made.

Pathologic Examination.—The crater of the large ulcer was seen; also a long black silk thread was found extending into the gastric cavity. Microscopic examination showed diffuse leukocytic infiltration and foci of large foreign body giant cells and fat-filled macrophages.

The patient was examined roentgenographically and gastroscopically after his second operation for gastrojejunal ulcer. At fluoroscopy the lesion was thought to have been seen but with no degree of certainty, whereas it was easily and clearly shown by gastroscopy. In regard to the fluoroscopist's statement that the stoma functioned well, it may be best to add here that a gastro-enterostomy stoma is said by the fluoroscopist to function well if the opening is patent. The gastroscopist speaks of normal function if the opening is patent and if rhythmic pylorus-like contractions are observed at the stoma. The fact that the opening allows the passage of food is not in itself sufficient. At the operation the ulcer was thought to be in the jejunum, 1 cm. from the stoma, whereas it was called a marginal ulcer at gastroscopy. In this case we are more inclined to believe the gastroscopic picture since these ulcers are always embedded in adhesions, and thus their exact location is often difficult to determine at operation. Moreover, it is difficult to believe that the ulcer could have been seen so easily and to such a full extent had it not been situated on the marginal line. The finding of the silk sutures was important and will be discussed later.

CASE 15.—*History*.—A 31 year old man, seen on Aug. 30, 1934, had in 1924, because of a diagnosis of gastric ulcer, been on a Sippy diet, with marked improvement in his condition. The following year he had several hemorrhages, and in 1926 a gastro-enterostomy was done. In 1933 an emergency operation was performed because of perforation of the old ulcer. Since Aug. 26, 1934, he had had severe abdominal distress, tarry stools being noted occasionally.

Physical Examination.—Tenderness was noted in the epigastrium.

Roentgen Examination.—The roentgen picture offered suggestive but not conclusive evidence of gastro-jejunal ulcer. Seven gastroscopic examinations were done on this patient; one of them preceded a new operation, while the others followed.

Gastroscopy (September 6).—The antrum was well seen. The gastro-enterostomy stoma was hidden behind a fold of the posterior wall. Radial folds were seen converging toward this point. At a distance of about 1 cm. from the edge of the stoma a small flat grayish yellow ulcer was seen. The surrounding area was not inflamed. On the basis of the gastroscopic findings a diagnosis was made of flat erosion of the posterior wall near the gastro-enterostomy stoma but no associated gastritis.

Operation (September 30).—Extensive adhesions were found. The stomach had previously been divided at the pylorus and anastomosed into the jejunum by side to end anastomosis. No ulcer was found. Partial gastrectomy was done.

Pathologic Examination.—No visible ulceration was present. The mucosa was edematous, and there were small submucous hemorrhages just proximal to the connective tissue scar.

The patient was seen again on December 28 complaining of "sour belching" and pain between the shoulders. Roentgenography did not show any pathologic process. There were intervals when the patient felt quite well, but the distress would frequently recur. The histamine test at that time showed free acid up to 30. We shall briefly list the findings at gastroscopies performed on the following dates:

November 28: It was possible to see the interior of the jejunum. The folds running toward the edge of the gastro-enterostomy stoma were purplish red and definitely swollen; two shallow erosions were seen. All other parts of the mucous membrane were also swollen; in the parts near the cardia hemorrhages were seen.

December 12: The erosions previously described had disappeared, but the mucosa surrounding the artificial opening was still extremely swollen.

January 29: The stomach was so sensitive that it retained with difficulty the air introduced during the examination. The area surrounding the stoma was extremely red and covered with small nodules.

May 28: The color of the mucosa of the jejunum did not show its usual uniformity; there were many grayish spots in the red mucosa. Small nodules were seen in the suture line.

July 1: The inflammation of the jejunum and stomach showed great improvement.

October 23: The artificial opening seemed to be narrower than at the last examination. The borders were definitely reddened. Thick layers of gray mucus were seen firmly adherent to the surface of the entire body of the stomach. Just below the cardia some thickened nodules were seen.

This patient was observed through a series of seven gastroscopic examinations. Before his admission to the hospital there had been several hemorrhages. Two operations had been done, the second being for perforation of an old ulcer. At the first gastroscopy the anastomosis between the end of the stomach and the jejunum was mistaken for the pylorus. After operation the stomach is often greatly distorted, making orientation difficult; such mistakes are not infrequent. A small flat yellow erosion was seen which we believe does not correspond with the roentgen picture since small erosions cannot be seen roentgenographically. Resection was justified because these erosions frequently are the cause of extensive hemorrhages. These extremely small lesions could not be seen in the gross specimen because the lack of circulating blood made the color a uniform grayish red. Gastroscopic visualization of the erosion and the definite history of hemorrhages precluded any possibility of doubt as to the existence of the lesion. The resection was followed by the development of severe gastritis, which was observed over a period of eleven months. It improved somewhat but never completely healed.

Case 16.—*History.*—A patient of Drs. J. Meyer and Necheles, at the Michael Reese Hospital, was seen on May 27, 1935. Gastro-enterostomy was done four years before for ulcer. The patient's complaint at the time of the present examination was distress typical of that produced by ulcer.

Gastroscopy.—The pyloric region was seen. Much secretion containing air bubbles was seen passing into the antrum from the duodenum. The greater curvature of the antrum presented several small yellow and orange-red spots. Above the angulus on the lesser curvature larger red spots were seen. The gastro-enterostomy stoma was found on the posterior wall; the margin was well seen and did not show the presence of an ulcer. A true jejunal ulcer, however, could not be ruled out. The diagnosis on the basis of the gastroscopic picture was severe superficial gastritis, especially of the greater curvature of the antrum and of the upper parts of the lesser curvature.

Operation (Dr. Strauss).—No ulcer was felt. A resection was carried out

Pathologic Examination.—The gross examination (Dr. Saphir) revealed a gastro-enteric orifice measuring 4 cm. in diameter; the serosa in this region contained fine grayish white streaks. The mucosa of the stomach was smooth, pinkish gray and glistening. Minute petechial hemorrhages were present in various areas, and the mucosa of the jejunum was dark red and hemorrhagic. Microscopic examination (Dr. Schindler) revealed in some portions of the specimen thickened and dense connective tissue below the surface epithelium; in other areas an extensive cellular infiltration was seen between the upper layers of the mucosa. In some spots there was lymphocytic and plasma cell infiltration. The capillaries of only the most superficial part of the mucosa were found to be much enlarged. Some cells of the glands showed cloudy swelling and vacuolation.

This patient had had gastro-enterostomy performed four years before and was at the time of examination complaining of symptoms suggestive of ulcer; there was also a psychoneurotic element present. Gastroscopic examination demonstrated severe chronic gastritis but no ulcer. This finding is frequent in the postoperative stomach. The red spots which were seen were well explained by the greatly enlarged blood capillaries of the superficial parts of the mucosa.

CASE 17.—*History.*—A 52 year old man, seen on July 7, 1934, had been placed on medical management in 1930 because of a diagnosis of duodenal ulcer with moderate stenosis. In January 1931 gastro-enterostomy was done. In February 1933 the patient had a hemorrhage from a gastrojejunal ulcer, which again occurred on July 10, 1934. He was placed on medical management but still complained of a gnawing sensation in the epigastrium, and on December 10 hemorrhage occurred again.

Physical Examination.—The patient appeared to be pale. A small area of tenderness was found in the midepigastric region.

Laboratory Examination.—The blood showed 55 per cent hemoglobin and 3,425,000 red blood cells. The stools gave a 1 to a 4 plus reaction to the benzidine test for blood.

First Gastroscopy (December 21).—The gastro-enterostomy stoma was not found with the retrograde instrument. In the normal mucous membrane of the cordlike musculus sphincter antri two small hemorrhages were seen. There were many nodules on the lower parts of the posterior wall, and the mucous membrane in this region was reddish gray and contained numerous red spots. The opening of the jejunum was not seen. The diagnosis on the basis of the gastroscopic picture was hemorrhages in a normal mucous membrane and severe chronic gastritis of the lower parts of the posterior wall.

Second Gastroscopy (December 27).—This time the usual straight tipped instrument was used, and the artificial opening was instantly found. It was possible to see the greater part of its edge and to look into the jejunum. The inflammation, seen on previous examination, was definitely improved. There was a polyp-like node overhanging the upper edge of the artificial opening, the mucous membrane of which was somewhat swollen and extremely reddened.

Roentgen Examination (December 28).—No jejunal ulcer was seen.

Second Operation (Jan. 2, 1935).—No ulcer was found. The line of anastomosis between the stomach and the jejunum was cut away. The artificial stoma was closed, and the ends of the divided jejunum were anastomosed.

Pathologic Examination.—The line of anastomosis showed no inflammation in the msucular wall, nor did the sections demonstrate an ulcer. Microscopic examination (Dr. Schindler) showed extensive interstitial infiltration of the mucosa with plasma cells, round cells and some eosinophils. The cells of the surface epithelium showed vacuolation and cloudy swelling. In certain areas the capillaries in the superficial layers of the mucosa were much enlarged. Occasional rupture of the vessels was seen with resultant hemorrhages. Infiltration of the submucosa was noted in some areas (fig. 11).

Third Operation (January 12).—Another operation became necessary because of the formation of a dense band of fibrous tissue, causing almost complete obstruction of the first part of the jejunum. Recovery was uneventful.

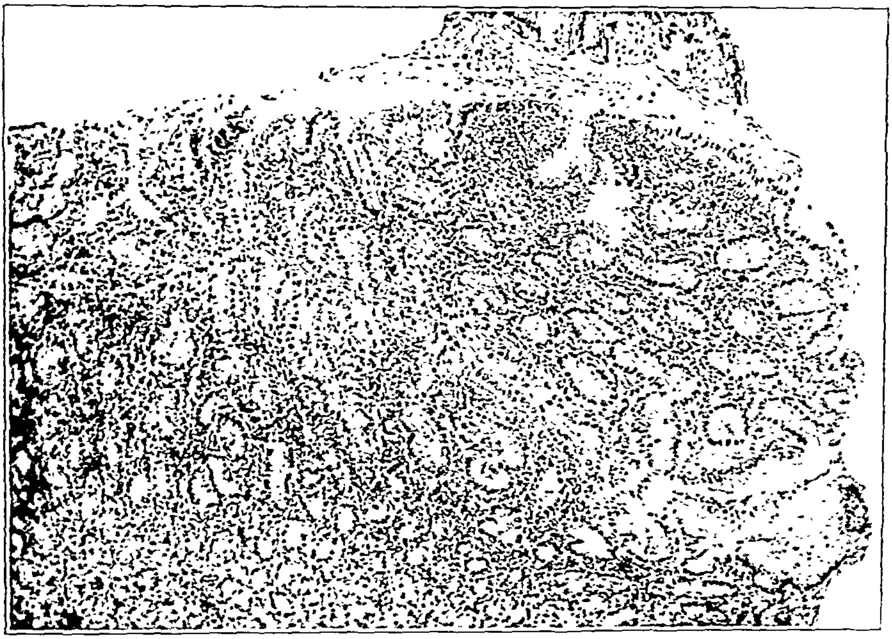

Fig. 11 (case 17).—Photomicrograph of a section made through the gastric mucosa after reoperation. Interstitial infiltration and exudation are well seen. The enlarged capillaries, *strikingly seen in the microscopic specimen, do not show* well in the reproduction.

Nine months later the patient complained of nausea and vomiting. He was placed on the Winkelstein treatment and was reported on November 8 to have been doing well.

Roentgen Examination.—The antrum showed a deformity which was probably the result of the old operation.

Third Gastroscopy.—An artificial opening was seen toward which folds of mucous membrane were converging. Above the opening one pigment spot and several small red spots were seen. The diagnosis on the basis of the gastroscopic picture was a postoperative stomach with a functioning stoma. The general condition showed surprising improvement after the second operation. Small hemorrhages and one pigment spot were seen in normal mucous membrane.

The patient originally had a duodenal ulcer, for which a gastro-enterostomy was done. Several hemorrhages occurred during the following four years. No ulceration could be found by roentgen examination or gastroscopy or at operation. Severe gastritis was then demonstrated by gastroscopy. After this the gastro-enterostomy stoma was closed; at the operation the ulcer was found to be healed. At the third gastroscopy the severe gastritis found previously had almost entirely healed. The mucous membrane, however, showed changes which were consistent with an ulcer of the stomach. The pigment spot should be considered as being a marked preulcerative or postulcerative condition. This case demonstrates a fact that we have previously observed; that even extensive hemorrhages occurring in a postoperative stomach may be caused by a severe gastritis which is frequently mistaken for an ulcer. Moreover, this case demonstrates that postoperative hemorrhagic gastritis may heal if the gastro-enterostomy stoma is closed.

Case 18.—*History.*—A 53 year old woman had had gastro-enterostomy done nineteen years previously for gastric ulcer. Her present complaint was localized epigastric pains.

Physical Examination.—There was moderate tenderness in the left upper quadrant 2.5 cm. from the umbilicus, but no other significant findings.

Laboratory Examination.—The stools gave a negative to a 3 plus reaction to the benzidine test for blood.

Gastroscopy (July 22).—The stomach was well seen. The angulus was so situated as to allow us to see the entire lesser curvature of the antrum. Just above the musculus sphincter antri on the anterior wall several small nodules were seen. At a higher level on the posterior wall the gastro-enterostomy stoma was seen. It could not be well observed since it was filled with a secretion of bloody mucus and air bubbles which was being expelled into the stomach from the jejunum. The presence of a gastrojejunal ulcer could not definitely be determined. The upper parts of the anterior wall were markedly swollen and contained small hemorrhages and nodules. The diagnosis on the basis of the gastroscopic picture was nodular hemorrhagic gastritis in a postoperative stomach. There was a bloody secretion from the gastro-enterostomy stoma.

Roentgen Examination (July 6).—Two of the views suggested the presence of a small fleck on the jejunal side of the gastro-enterostomy stoma. The rugous folds of the jejunum were thickened and distorted. Flecks at the gastrojejunal opening were extremely hard to evaluate because of operative pockets, but in view of the clinical findings we saw no reason to doubt that the fleck seen at fluoroscopy and on the films was anything other than the crater of an ulcer. The picture suggested gastrojejunal ulcer with jejunitis.

Operation (August 7).—An indurated area of a diameter of 1 cm. could be felt on the distal loop of the jejunum immediately at the anastomosis. Resection plus posterior polyanastomosis was done. The patient died on August 7.

Pathologic Examination.—The specimen consisted of a section of the intestinal tract measuring, when laid open, 15 by 10 by 1 cm. The serosa was thick and fibrous. The muscle coats were distinct and well developed. The mucosa was edematous and hyperemic. The stoma of the enterostomy was red and smooth. There was little or no evidence of inflammation or ulceration. Microscopic examination of sections through the edge of the stoma showed chronic inflammation of the muscularis and some atypical glandular proliferation at the stoma. There was no frank evidence of neoplasm.

The clinical impression in this case was that the lesion was a jejunal ulcer. Although the roentgenologist stated that it was difficult to differentiate between a jejunal ulcer and a postoperative pocket, he concluded that a fleck was present. Gastroscopy did not permit good visualization of the jejunum but did reveal frank hemorrhagic gastritis. A thickened area was found at operation which was assumed to be the clinically diagnosed jejunal ulcer. Pathologic examination proved that no ulcer was present but that gastritis could be demonstrated microscopically. This case illustrates that roentgenographic examination, examination of a gross specimen or a gastroscopic examination is not infallible. The gastroscopic findings, however, were the most accurate in that they showed the presence of the inflammatory changes which were seen microscopically. It is, of course, possible that an ulcer in the lower part of the jejunum was overlooked at operation; this is not probable, however. Unfortunately autopsy could not be carried out.

CASE 19.—*History.*—A 45 year old patient, seen on Nov. 29, 1934, had an uncomplicated duodenal ulcer in March 1932. In December 1932 a posterior gastro-enterostomy was done because of considerable stenosis. A recurrence of epigastric distress developed in June 1934. This continued until two weeks previous to admission, at which time the patient noticed considerable epigastric distention. Five days before admission a severe cramplike pain developed across the epigastrium. Since that time the pain had recurred daily and had also been present at night.

Physical Examination.—No significant findings were noted.

Laboratory Examination.—The gastric fluid showed: free acid, 36, and total acid, 60. The stools gave a 1 to a 4 plus reaction to the benzidine test for blood.

Roentgen Examination (November 28).—The roentgen picture was negative for gastrojejunal ulcer.

Gastroscopy (November 22).—The interior of the jejunum was well seen; the complete circumference of the artificial opening could be observed. No ulcer and no peristalsis was observed. The folds were delicate, but the areas between the folds showed a grayish color. The diagnosis on the basis of the gastroscopic picture was rigidity of the artificial opening between the stomach and the jejunum and superficial gastritis.

Operation (December 13).—There was no stenosis of the duodenum. The gastro-enterostomy stoma was closed, and two large jejunual ulcers were excised. One of them was found to be directly in the suture line and had perforated the jejunum, its base lying against the transverse colon. The other ulcer lay about 2 inches (5 cm.) distal to the opening into the jejunum. The stoma of the previous gastro-enterostomy was closed.

Pathologic Examination.—There was a rather marked inflammatory reaction, with diffuse and focal round cell infiltration, and occasional areas of leukocytes were seen. No ulcer was found.

The patient was discharged, but in February pains again developed in the right side of the abdomen. These were most severe at night.

Roentgen Examination.—The roentgenogram of the stomach was normal. There were multiple diverticula of the sigmoid colon.

Second Gastroscopy.—In the pyloric region an opening was seen which was probably the pylorus itself. No other opening was seen. There was a circumscribed area on the surface of the posterior wall which contained thick layers of mucus. The other portions of the mucous membrane were normal. The patient was placed on medical management for ulcer on March 20, 1935, and felt "like a different person."

The explanation of this case is not entirely satisfactory. Two and a half years after gastro-enterostomy for duodenal stenosis, new pains developed. An ulcer could not be demonstrated by roentgen examination or gastroscopy or later by the pathologic studies. However, the surgeon who closed the gastro-enterostomy stoma found two large ulcers. Microscopic examination confirmed the gastroscopic diagnosis of chronic gastritis. Later, symptoms again appeared which were thought by the clinician to be of psychic origin and which completely disappeared on treatment for ulcer. We should probably assume that the observation of the surgeon was correct, in which case we have demonstrated a fact which is well known, namely, that jejunal ulcers may be overlooked by both roentgenographic and gastroscopic examinations.

Case 20.—*History.*—A patient of Drs. L. Meyer and Necheles, at the Michael Reese Hospital, was seen on May 27, 1935. He had undergone resection f gastric ulcer one year before and at the present admission gave a typical histo of ulcer.

Gastroscopy.—In spite of a marked kyphosis, the examination was carried o without difficulty. The jejunum was seen for an extent of about 5 cm. Th Kerkring folds were seen so well that the presence of a deep jejunal ulcer coul be ruled out in this case. The margin of the opening lying toward the greate curvature was somewhat swollen, and at the side of the anterior wall a smal shallow, yellow erosion was observed. The parts of the stomach lying abov the opening showed marked changes consisting of red spots and layers of mucus The mucous membrane was sensitive in this region. The diagnosis on the basi of the gastroscopic findings was postoperative stomach and severe gastritis of the mucous membrane with a superficial erosion of the artificial opening. The jejunum was fully visualized.

Operation (Dr. Strauss).—No lesion could be demonstrated from the outside.

The patient had previously had a gastric resection done, after which severe gastritis with marginal erosion developed. The symptoms were typical of a recurrent or jejunal ulcer. It is easy to understand that the surgeon could find nothing from the outside, since gastroscopy showed no ulcer to be present. Another resection certainly would have brought no relief to the patient. We should probably have presented this case in our next group since the stomach was not opened, i. e., those cases without biopsic control. We wish to point out, however, that the findings of the surgeon agreed with those of the gastroscopist in that no real ulcer was present.

POSTOPERATIVE STOMACH WITHOUT BIOPSIC CONTROL

The cases of postoperative stomach without biopsic control offer so many interesting observations that they should not be omitted. However, we shall present them as briefly as possible in the following rough classification: (1) normal or fairly normal mucosa, (2) slightly abnormal mucosa, (3) recurrent ulcer, (4) jejunal ulcer, (5) simple erosions, (6) jejunal ulcer plus silk sutures, (7) silk sutures plus gastritis, (8) chronic gastritis, (9) gastritis plus perigastritis, (10) gastritis resulting from high voltage roentgen therapy and (11) unsatisfactorily explained cases.

Normal or Fairly Normal Mucosa.—CASE 21.—*History.*—A 40 year old woman had indefinite distress and pains and gas in the abdomen. She had formerly had a gastro-enterostomy done.

Physical Examination.—Abdominal scars and a large ventral hernia were noted.

Roentgen Examination.—The picture revealed a normal stomach.

Gastroscopy.—With the gastroscope introduced deeply, a mouthlike opening was seen in which circular folds appeared on its mucous membrane. When the instrument was withdrawn somewhat, the antrum appeared so that it was possible to observe the antrum, pylorus and artificial opening in the same visual field. The artificial opening contracted rapidly and closed completely (fig. 12) every fifth or sixth second. Its activity was entirely different from that of the pylorus. The antrum was limited by a marked musculus sphincter antri which was cordlike, whereas the lips of the artificial stoma were smooth, the upper one of which passed gradually into the mucous membrane of the posterior wall. Above the angulus thick gray mucus was seen lying between the folds of the greater curvature and the anterior wall; the upper parts of the stomach were normal. The diagnosis on the basis of the gastroscopic findings was rhythmic contractions of the gastro-enterostomy stoma in the posterior wall of the antrum of a type different from the contractions of the pylorus and slight superficial gastritis of the lower portions of the body of the stomach. (See *G* in the color plate.)

If one observes the postoperative stomach of a patient who has no complaints one usually sees an artificial opening with a pylorus-like rhythm. In this case the opening had its own peculiar rhythm of a type which we have never seen before. It is possible that this atypical action was responsible for the development of the superficial gastritis, which was slight. The patient's symptoms were probably caused by the ventral hernia with its adhesions plus a certain amount of apprehension.

CASE 22.—*History.*—A patient of Drs. J. Meyer and Necheles, at the Michael Reese Hospital, had undergone resection of the stomach for gastric ulcer.

Gastroscopy.—A shallow cavity was seen at the end of the stomach. A dark hole which contracted rhythmically was observed at the end of this cavity. The edges of this hole were covered with some mucus, but there was no ulcer. All other parts of the stomach were normal. The diagnosis on the basis of the gastroscopic findings was rhythmic action of the artificial opening between the stomach and the intestine, but no ulcer or gastritis.

This case demonstrates that even in a stomach which has been resected it is possible that a rhythmic pylorus-like action may develop in the artificial opening, although it is so rare that this is the first time it has been described. The important observation is that no gastritis was present, which tends to confirm our belief that postoperative gastritis is the result of improper functioning of the artificial opening.

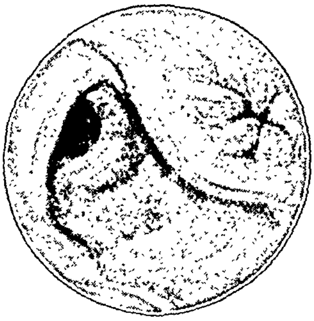

Fig. 12 (case 21).—Gastroscopic picture of a gastro-enterostomy stoma with functional adaptation. The same stoma is pictured in *G* of the color plate, but there the objective of the gastroscope was turned toward the posterior wall, and therefore only the gastro-enterostomy opening is seen. In this figure the pylorus and the gastro-enterostomy stoma are seen in the same visual field; the pylorus is open, and the stoma is closed with a stellar formation. A small portion of the pylorus was hidden behind the *angulus*. The greatest portion of the antrum is visible. It is evident that the gastro-enterostomy stoma lies close to the antrum.

CASE 23.—*History.*—A patient of Drs. J. Meyer and Necheles, at the Michael Reese Hospital, had undergone resection of the stomach for gastric ulcer. The complaints at the present examination were suggestive of gastrojejunal ulcer.

Gastroscopy.—A spasm was felt at the lower pole, which soon relaxed, allowing good visualization. The artificial opening was seen; three fourths of its margin was quite smooth, but the remaining quarter, which lay toward the greater curvature, was nodular. *The intestine with the Kerkring folds was well seen.* Both loops were observed; they were separated by a definite ridge. *The anterior* loop showed peristaltic waves. There was no ulcer or inflammation in or near the jejunum. After the examination the patient appeared to be very nervous and complained of pain in her stomach. The diagnosis on the basis of the gastroscopic findings was no jejunal ulcer, slight gastritis in the uppermost parts of the stomach and tonic spasms of the stomach.

In spite of the fact that this opening was not entirely pylorus-like in its action, there was no severe inflammation and no ulceration. The spasm, together with the patient's general nervous temperament, seems to indicate that a psychoneurosis associated with painful spasms was responsible for her symptoms.

Slightly Abnormal Mucosa.—CASE 24.—*History.*—A 26 year old woman, seen on July 6, 1934, had had frequent hemorrhages from 1925 to 1935. Gastro-enterostomy was done in August 1928, and in October 1928 the stoma was closed.

Roentgen Examination (November 20).—The picture was that of a duodenal ulcer and an old operative defect of the stomach (distortion of the folds).

First Gastroscopy (November 1).—The antrum was irregular in form. Radial folds were seen running toward the pylorus, which remained hidden under an irregularly bent fold. The fold was probably the angulus distorted by operation. Two small nodules were present on the anterior wall. The diagnosis on the basis of the gastroscopic findings was scar formation in a postoperative stomach and residuals of gastritis.

Second Gastroscopy (Feb. 1, 1935).—The picture was similar to that seen at the first gastroscopy.

The frequent hemorrhages were probably due to a duodenal ulcer. Four years previously the gastro-enterostomy stoma was closed. The stomach showed distortion caused by this operation and residuals of gastritis. This case demonstrates the good results often obtained by eliminating a gastro-enterostomy stoma.

Recurrent Ulcers.—CASE 25.—*History.*—A woman aged 32, seen on Jan. 19, 1935, had undergone gastro-enterostomy in 1930 for gastric ulcer. She felt well until March 1, 1934, when she complained of "gas around the heart" and cramplike pains, which usually settled in the upper left abdominal quadrant.

Physical Examination.—There was tenderness in the epigastrium.

First Roentgen Examination (January 19).—There was at least one, and probably two, penetrating ulcers on the lesser curvature immediately above the angulus. An old duodenal deformity was seen. The gastro-enterostomy stoma was patent. The possibility of an associated mild gastritis could not be ruled out.

First Gastroscopy.—The entire stomach, including the lesser curvature of the antrum, was seen. The pylorus functioned normally. At the depth of the angulus behind a fold of the posterior wall was seen the artificial opening of a gastro-enterostomy which showed activity like that of a normal pylorus; e.g., when it closed it formed the well known stellar formation, and when it was open it showed a round hole. Since both openings could not be seen in the same visual field, it could not be observed whether the rhythm was the same. The mucous membrane of all these parts was normal. Above the angulus, along the lesser curvature yellowish gray, irregular ulcerations were seen. Most of them did not give the impression of being deep; the crater-like appearance was missing, and yet they did not resemble the ulcerations of typical gastritis ulcerosa; six of these ulcers were counted. The surrounding mucous membrane did not show marked inflammation, although the edges of the ulcers were somewhat reddened. The diagnosis on the basis of the gastroscopic findings was numerous shallow ulcers of the lesser curvature and pylorus-like activity of the gastro-enterostomy opening.

Second Gastroscopy (February 25).—All ulcerations had completely disappeared. On the anterior wall was seen a small dark brown erosion (which had the typical appearance of the so-called "hemorrhagic erosion"). In the highest parts of the lesser curvature red spots were seen which were not sharply limited. In the surrounding pale area a big brown pigment spot was seen. The diagnosis was one small hemorrhagic erosion in the anterior wall, a large pigment spot and completely healed ulcerations.

Second Roentgen Examination (February 28).—The penetrating ulcer formerly present at the lesser curvature of the stomach had disappeared.

Third Gastroscopy (May 16).—The Kerkring folds and the whole margin of the stoma were seen. Two small mucosal hemorrhages were present, but the hemorrhagic erosion had disappeared.

Fourth Gastroscopy (July 18).—The gastro-enterostomy opening was working rhythmically. There were no erosions, no hemorrhages and no pigment spots.

Because of the frequent gastroscopic observations, this case is particularly interesting. The patient did not have a history that was typically suggestive of ulcer. Roentgen examination revealed the old gastro-enterostomy stoma and one or two ulcers of the lesser curvature. Gastroscopic examination demonstrated that the gastro-enterostomy opening worked rhythmically and in a pylorus-like manner. It demonstrated further the presence of six ulcers of the lesser curvature with no gastritis. The ulcerations all healed completely in one month under medical management. The typical hemorrhagic erosion in an otherwise normal stomach which was seen is a frequent finding in "ulcer stomachs." We feel certain that Konjetzny[15] would not have denied their existence if he had performed gastroscopy on his patients. Some months later the stomach was normal except for the presence of two small hemorrhages; these are also frequently seen in "ulcer stomachs." They may change into pigment spots or into hemorrhagic erosions and finally into ulcer. The excellent result of medical treatment in this case was remarkable. The fact that there was no gastritis present was probably because of the rhythmic pylorus-like function of the gastro-enterostomy opening.

Jejunal Ulcer.—Case 26.—*History.*—A 58 year old man, seen on Oct. 24, 1934, had a condition which was diagnosed as duodenal ulcer with obstruction on Feb. 12, 1929. An anterior gastro-enterostomy was done. On July 26, 1932, a second operation was done, at which numerous bleeding jejunal ulcers were found. A part of the jejunum was excised, and the jejunum and stomach were closed. Ulcerated hemorrhagic areas were observed in the intestine.

On Aug. 1, 1933, duodenal ulcer with a high grade of stenosis was again found. Partial gastrectomy was done on August 4. Two ulcers of the stomach were observed. On Oct. 24, 1934, the patient again presented himself, complaining of having had severe pain daily in the left abdominal quadrant.

Physical Examination.—Tenderness was elicited in the left upper quadrant.

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[15] Konjetzny, G. E.: Die entzündliche Grundlage der typischen Geschwürsbildung im Magen und Duodenum, Berlin, Julius Springer, 1930.

First Roentgen Examination (Oct. 26, 1934).—A large recurrent ulcer was seen at the lesser curvature of the gastric stump.

First Gastroscopy (October 27).—The examination was unsatisfactory. The artificial opening was seen, and no peristaltic movements were observed. There was a small area of superficial gastritis.

Second Gastroscopy (December 7).—The picture had changed completely. The new opening was seen, and on its upper edge there was a deep ulcerated crater the floor of which was covered with whitish yellow layers and the edges of which were extremely reddened and hemorrhagic. The folds of the mucous membrane as well as the valleys between them were covered with yellowish layers of pus. The mucous membrane surrounding the opening was exceedingly swollen and reddened. In the upper parts of the stomach the folds became thin, their ridges were red, and the valleys between them were grayish red. The diagnosis on the basis of the gastroscopic findings was a deep marginal ulcer and suppurative hypertrophic gastritis surrounding the opening. (See *H* in the color plate.)

Third Gastroscopy (December 13).—The ulcer was seen better than at the previous examination. It was quite evident that it was situated in the wall of the jejunum itself. Its edges were reddened, and whitish layers of mucus were seen on one side of the edge. The surrounding mucous membrane, however, was no longer as extremely swollen as it was during the previous examination. The diagnosis on the basis of the gastroscopic findings was jejunal ulcer and improvement of the associated inflammation.

Second Roentgen Examination (December 29).—An ulcer at the region of the gastric anastomosis could no longer be demonstrated.

Fourth Gastroscopy.—The examination was unsatisfactory. There was so much mucus and secretion present that the jejunum was not seen.

Fifth Gastroscopy (Jan. 30, 1935).—The jejunum and ulcer were seen instantly with the straight tipped instrument. The ulcer was shallow and yellowish, and the surrounding area was not swollen. There was no secretion present. The diagnosis on the basis of the gastroscopic findings was a healing jejunal ulcer and no gastritis or jejunitis.

Sixth Gastroscopy (March 5).—The opening appeared to be narrower. The border could be well seen; there was a small grayish scar, but no ulcer was present nor was any inflammation seen. The diagnosis was apparent healing of the ulcer and gastritis.

Seventh Gastroscopy.—Visualization was excellent. Slight superficial gastritis was seen, and the ulcer was healed.

Eighth Gastroscopy (May 2).—The first 2 to 3 cm. of the jejunum was well seen. No ulcer or inflammation was present. On the side opposite where the previously seen jejunal ulcer had been a small but definite yellowish patch was observed which remained constant during the entire examination. The mucous membrane of the stomach was essentially normal. The yellow spot might have represented the beginning of a new jejunal ulcer.

Ninth Gastroscopy (July 5).—The picture was similar to that seen on the last examination. There was considerable secretion in the jejunum, and the mucosa was somewhat inflamed, but there was no ulceration either in the stomach or in the jejunum.

Tenth Gastroscopy.—The jejunum appeared to be normal. The inflammatory changes were much improved over those seen at the last examination. There seemed to be a cobble-stone appearance of the mucous membrane of the fornix. No ulcer was seen. The jejunum was well visualized, and there was a small residuum of inflammation.

After the patient underwent several operations a jejunal ulcer developed. It was possible to watch the progress by a series of ten gastroscopies in spite of the fact that he was stout and had an unusually sensitive gastric mucosa. The excellent visualization of the ulcer in the interior of the jejunum was unusual. The healing of the ulcer under medical management (Winkelstein tube) was most interesting to watch. Gastroscopy in this particular case was definitely superior to roentgen examination.

Simple Erosion.—These lesions have been seen in two preceding cases to which we refer the reader. In case 19 an erosion without gastritis was observed which, of course, was not seen in the gross specimen after resection. Later gastroscopies were done in this case, which demonstrated similar erosions. Finally, a severe inflammation developed.

A typical hemorrhagic erosion was observed in case 25 in a noninflamed mucosa after the healing of six true ulcers of the lesser curvature. This erosion healed without consequence.

Jejunal Ulcer and Silk Sutures.—In case 14 the large silk sutures were found in the gross specimen hanging into the cavity of the stomach. It might be assumed that the presence of these sutures was of consequence in the development of the jejunal ulcer. This, however, cannot be proved.

Silk Sutures Plus Gastritis.—The following four gastroscopic examinations which have not yet been cited were done in case 1, after resection of a benign obstructing ulcer of the duodenum.

Second Gastroscopy (Sept. 21, 1934).—There was a high wall seen which separated the body of the stomach from a round black hole, which apparently was the artificial opening. Toward the anterior side there was a mushroom-like elevation, the middle of which was drawn in and appeared to be puckered. A black silk thread was seen which had not cut through the mucous membrane.

Third Gastroscopy (November 1).—All findings of a superficial gastritis were observed. Many red spots were seen, and large collections of mucus lay between the folds. The artificial opening was open and rigid. Silk threads were well seen.

Fourth Gastroscopy.—It was possible to penetrate into the jejunum with the gastroscope, so that a long portion of it was well observed; it was found to be normal. The wall of the opening was thick and somewhat reddened. Above this point in the anterior wall there were two sutures (silk threads) which were hanging partially free into the interior of the stomach. The areas surrounding them were spotted and covered with mucus.

We were unable to follow the patient further because he had to return to his home in Canada, but it is important to note that gastritis was observed surrounding the sutures.

CASE 27.—*History.*—A patient of Dr. J. Meyer, at the Michael Reese Hospital, had a gastro-enterostomy done for gastric ulcer on Aug. 5, 1935. He later complained of pain in the left upper abdominal quadrant.

Gastroscopy.—The antrum was normal. There was a black silk suture in the lowest part of the posterior wall which had cut through the mucous membrane at the side of a fold, behind which probably lay the gastro-enterostomy stoma. In the upper parts of the posterior wall some small nodules were observed. Just below the cardia there was a network of blue blood vessels lying in an area having a greenish gray color. One hemorrhagic spot was observed between the nodular part and the discolored area. The diagnosis on the basis of the gastroscopic picture was the presence of a black silk suture which had cut through the mucous membrane and hypertrophic and atrophic gastritis of the upper parts of the body.

These silk sutures which have penetrated the mucous membrane cause a severe gastritis, often with erosions, and although it seemed possible that those in case 1 may have been expelled eventually, they usually have to be removed surgically. When this is done the patient often becomes entirely free from symptoms. For these reasons we believe that the presence of sutures which have penetrated the mucous membrane constitutes a definite indication for operation.

Chronic Gastritis.—In 1922 one of us (R. S.) [14] described the frequency, importance and seriousness of chronic gastritis in the postoperative stomach. Following this, all gastroscopists and later many surgeons and internists agreed that chronic gastritis is mainly responsible for the distress so frequently found after operations for gastric lesions. Since chronic gastritis seems to develop much more frequently in those cases in which the action of the artificial opening is not pylorus-like, we may assume that the intestinal juice flowing into the stomach through this patent opening is in some way responsible for the origin of most of these severe gastritides. It may be dependent on a chemical or a bacteriologic influence, or it may be the result of a combination of these factors. It is true that the gastritis may sometimes be present before the operation, but by observations cited in this paper it becomes evident that there are cases in which there was no gastritis previous to operation (case 19) and in which it developed to a severe extent postoperatively. Evidence seems to indicate further that this type of gastritis may be healed by eliminating a gastro-enterostomy stoma (case 16). The classification of chronic gastritis into three divisions (superficial, hypertrophic and atrophic) does not hold in the postoperative stomach. Henning has tried to sustain this classification, but since all combinations are seen and the prognosis is always the same, e. g., the gastritis heals only rarely and then usually in cases in which the gastro-enterostomy opening has been eliminated, we shall not attempt to do so. There is no great difference between the pictures of the gastritis found in the stomach which has been resected and in the stomach in which a gastro-enterostomy has been done. We find, however, in a study of a great number of cases, that the opening of the gastro-enterostomy more frequently shows the rhythmic pylorus-like action than does the opening of the stomach which has been resected. A gastro-enterostomy is advantageous in that the stoma can be closed if necessary.

Before presenting any additional cases, we shall refer to four cases already reported (cases 15, 16, 17 and 19). Case 15 presented symptoms which were typical of an ulcer after a gastro-enterostomy had been done. Gastroscopically and microscopically, a severe gastritis without ulcer was found. In case 16, in which a gastro-enterostomy was also done, frequent hemorrhages occurred. At gastroscopic examination no ulcer was found, but a severe gastritis was seen. At the following operation no ulcer was demonstrated and the old duodenal ulcer seemed to be healed; the gastro-enterostomy opening was closed. After this the gastritis healed.

In case 17 it was thought, on the basis of the clinical picture, that a jejunal ulcer developed after gastro-enterostomy. Gastroscopic and microscopic examinations showed the nonexistence of an ulcer and demonstrated the presence of severe gastritis.

In case 19 there was a shallow erosion with some hemorrhages but no gastritis. After resection severe gastritis developed.

CASE 28.—*History.*—A patient presented a history of ulcer since 1922. Gastro-enterostomy was done in 1922 and undone in 1928. Uncomplicated duodenal ulcer occurred in 1929; resection of the pylorus was performed in 1932 for the duodenal ulcer and in 1933 for a jejunal ulcer (pathologically confirmed). The patient was seen on April 13, 1935, because of recurring epigastric distress. He had suffered from pain in the right shoulder for the past four months. The distress had been present since the last operation.

Physical Examination.—A number of abdominal scars were present. No tenderness was elicited, and the liver was just palpable.

Roentgen Examination.—There was no definite evidence of fleck in the stomach. The patient localized his tenderness to the point of the anastomosis. The appearance of the rugous folds was suggestive, but not conclusive, of gastritis.

Laboratory Examination.—The gastric contents showed free acid up to 122 by the histamine test.

First Gastroscopy (October 5).—The opening into the jejunum was well seen; its mucous membrane and that of surrounding areas of the stomach was reddened and showed many irregular nodules and hemorrhages. These changes were also present in the upper parts of the stomach, but to a lesser extent. The diagnosis was hypertrophic hemorrhagic gastritis in a postoperative stomach.

Second Gastroscopy (Jan. 29, 1935).—The artificial opening was completely rigid. There were no great changes from the previous examination. The secretion of mucus and pus was more extensive than before, especially in the jejunum where all the valleys between the Kerkring folds were covered with a thick secretion. The mucous membrane of the stomach was extremely red.

Three more gastroscopic examinations were carried out on the following dates: March 13, April 20 and July 15. Each of these demonstrated the picture that has already been described. The patient was given the Winkelstein treatment, and although his distress seemed somewhat less at times it always recurred with its usual intensity.

A gastric resection was done on this patient after several previous operations had been carried out. An ulcer was found at the time of resection, but no gastritis was present. After operation marked gastritis developed, which was well observed through a series of six gastroscopies. A recurrent ulcer could not be demonstrated either by roentgen examination or by gastroscopy. In contrast to case 26, in which a recurrent ulcer was present, in this case there was no response to the Winkelstein treatment. The case illustrates the poor prognosis offered by gastritis in a stomach after resection.

Case 29.—*History.*—A 60 year old man, who had undergone resection of the stomach for carcinoma in 1930, was seen on Oct. 21, 1935. For the past two to three months he had complained of pain, nausea and anorexia.

Roentgen Examinations (Six).—There was no evidence of obstruction. Gross dilatation of the intestinal coils was noted in the small intestine.

Gastroscopy (November 11).—The artificial opening was easily seen. In the upper parts of the stomach some small patches of thick mucus were observed. Just below the cardia the mucous membrane became thin, and two large blood vessels were seen. The diagnosis on the basis of the gastroscopic findings was atrophic and superficial gastritis of a slight degree in the upper parts of the stomach. The patient's condition might be expected to run a favorable course.

The atrophic form of gastritis is not frequently seen in a stomach after resection. In this case it may have been present before resection, accompanying the carcinoma, which was removed five years previously. Here are seen the good results which may be expected from early surgical removal of a carcinoma of the stomach.

Case 30.—*History.*—A 56 year old man had undergone subtotal resection for peptic ulcer in 1924 at the Cook County Hospital. He had had an intermittent burning type of distress in the epigastrium ever since. This was not relieved by the ingestion of food and little by the ingestion of alkalis. During the past two years it had become worse. The patient was seen on Aug. 19, 1934.

Physical Examination.—There were epigastric tenderness and a systolic murmur at the base of the heart.

Laboratory Examination—The gastric fluid obtained after an Ewald test meal showed: free acid, 0, and total acid, 16.

Roentgen Examination.—Two gastrojejunal ulcers were probably present with marked thickening of the gastric mucosa.

Gastroscopy (August 22).—The jejunum and its folds were easily seen. A brown silk thread was noted near the operative opening which had not cut through the mucous membrane. Hypertrophic changes were seen on the anterior wall in the superior parts of the stomach; there were also small hemorrhages and some edema. At one point there was a distinct erosion, which was very shallow and which had a whitish base. Other parts of the stomach were normal. The diagnosis was hemorrhagic hypertrophic gastritis after resection.

The distress of which the patient complained was undoubtedly due to the marked hypertrophic gastritis which was found to be present.

The following two cases of gastritis after resection show definite signs of perigastritis. The first of them was further complicated by gastric hemorrhage.

Case 31.—*History.*—A 37 year old man, seen on May 10, 1935, gave a history of epigastric distress of long duration which was suggestive of ulcer. Partial gastrectomy was performed in November 1932, after which a hemorrhage occurred. The patient was again operated on on Feb. 3, 1935, for jejunal ulcer. He stated that he had recently had another hemorrhage.

Physical Examination.—No significant findings other than numerous abdominal scars were noted.

Roentgen Examination (June 17).—There was no definite evidence of an ulcer crater.

Laboratory Examination.—The histamine test of the gastric fluid showed free acid up to 72.

First Gastroscopy (May 11).—The examination was unsatisfactory because of the poor cooperation of the patient. Hypertrophic gastritis was seen.

Second Gastroscopy (May 14).—The patient was quiet, and the anterior margin of the artificial opening was well seen. Beyond it the mucous membrane of the stomach prevented visualization of the posterior margin and the jejunum itself. The mucous membrane of the margin and that surrounding it was red and swollen; creases were seen. There were marked defects in the epithelium which were so small that they could scarcely be called ulcerations. Spots of mucus were observed in the lower parts of the stomach. The diagnosis was postoperative distortion of the entire stomach (Moutier would call this "perigastritis" and would probably be correct in doing so) and severe erosive hypertrophic gastritis. A jejunal ulcer could not be ruled out; however, the small erosions could account for the bleeding.

Third Gastroscopy (July 15).—The examination was unsatisfactory since the wide-angled instrument was not available.

Fourth Gastroscopy.—This gastroscopy was done at the patient's request. The entire stomach was well seen. The artificial opening was observed, but a small part of its edge could not be seen. The mucous membrane of the jejunum appeared to be normal. The edge of the stomach was markedly reddened and swollen; the folds in the body were serpiginous. A solitary reddened node was seen in the midportion of the greater curvature. Thick grayish white mucus was observed between the folds just below the cardia. There was improvement in the hypertrophic gastritis.

The patient presented a history of ulcer of long duration for which partial gastric resection was done. Later, a complete examination was done after an extensive hemorrhage. No ulcer was found, but gastroscopy revealed severe erosive hypertrophic gastritis. Although an ulcer could not be ruled out with certainty, it is most likely that the hemorrhage was caused by the erosions. There was evidence of perigastritis. The gastritis improved but did not disappear completely.

Case 32.—*History.*—A 64 year old man, seen on Nov. 2, 1935, two years previously had amebic dysentery. About a year before a gastric resection was done for peptic ulcer. The present complaint was anorexia and loss of weight. The patient wished a complete check to rule out carcinoma.

Laboratory Examination.—The gastric fluid after an Ewald test meal showed: free acid, 0, and total acid, 35. The stools were normal.

Roentgen Examination.—There was no evidence of a lesion in the gastric resection; the stoma functioned well.

Gastroscopy.—Orientation was difficult because of the extreme postoperative distortion. In the lowest part of the stomach there were many serpiginous folds between which many nodules were seen. In the area probably corresponding to the old suture line a hemorrhagic node and thick layers of mucus were seen. At a higher level the folds of the greater curvature were seen, and toward the anterior wall appeared the oval dark opening of the gastro-enterostomy. Dr. Renshaw thought that he saw circular folds within this opening, but they could be seen only at the moment of the height of inspiration. In the upper parts of the stomach one hemorrhagic node and many smaller nodules were obeserved. The diagnosis was greatly distorted postoperative stomach; hemorrhagic, nodular, hypertrophic gastritis, and a patent artificial opening.

It is doubtful whether this patient ever had an actual ulcer. A large resection was done, however, and when he presented himself at the clinics he complained only of anorexia and loss of weight. The clinical examination gave negative results. Gastroscopy revealed hypertrophic gastritis and an extremely distorted stomach. Distortion is usually seen better by roentgen examination than by gastroscopy. In accord with Moutier, we did not hesitate to assume that perigastritic adhesions, which apparently did not bother the patient, were present.

Case 33.—*History.*—A 39 year old man, referred by Dr. B. Goldberg on Nov. 6, 1935, had a gastro-enterostomy performed seven years before; the surgeon found a duodenal ulcer. The patient's complaint at the time of the present examination was epigastric pain associated with cramps. He was relieved by eating. The region around the gastro-enterostomy stoma was not painful on manipulation before the fluoroscope.

Gastroscopy.—The antrum and the action of the pylorus were well seen. There was a marked cordlike musculus sphincter antri over the anterior wall. Toward the greater curvature and below this suture line the gastro-enterostomy opening was seen. It was patent but did not contract. As the instrument was withdrawn large nodes were seen on the posterior wall and some smaller ones on the anterior wall. The folds of the posterior wall were segmented, and a dark crease could be seen crossing one of them. A solitary node was seen on the lesser curvature.

The diagnosis on the basis of the gastroscopic findings was marked hypertrophic gastritis of the body of the stomach.

This case illustrates the usual sequela of a patient with a nonrhythmically working gastro-enterostomy opening, i. e., marked hypertrophic gastritis.

Case 34.—*History.*—A patient, referred by Dr. Federman, had had a gastro-enterostomy performed because of benign duodenal obstruction. His complaint at the time of the present examination was epigastric pain.

Gastroscopy.—The entire stomach was well seen. The greater curvature of the antrum showed large, tortuous, thickened folds, with some creases and hyperemic spots. There was no ulcer or inflammation in the area of the gastro-enterostomy stoma. The upper parts of the stomach were normal. A diagnosis of severe gastritis of the greater curvature of the antrum was made.

As in case 34, gastroscopy showed severe hypertrophic gastritis in a patient with a patent gastro-enterostomy stoma. Since the inflammation was restricted to the greater curvature in this case, it is possible that it may have originally been caused by the obstruction.

Case 35.—*History.*—A 43 year old man had had a gastro-enterostomy performed five years before the present examination. His present complaint was diarrhea persisting for five weeks, belching and epigastric distress. He stated that he felt better if he did not eat.

Physical Examination.—There were no significant findings.

Laboratory Examination.—The gastric fluid after an Ewald test meal showed: free acid, a trace, and total acid, 60. The stools gave a 1 plus reaction to the benzidine test for blood.

Roentgen Examination.—The gastro-enterostomy stoma was patent. No jejunal ulcer was demonstrated.

Gastroscopy.—The pylorus was well seen; across the greater curvature of the antrum ran a solid narrow fold. On the posterior wall near the pylorus there was an opening through which the interior of the intestine was easily seen. The new opening did not close during the peristalsis. The lower border of the gastro-enterostomy stoma showed definitely reddened areas, as did also the folds of the anterior wall. There were many small nodules in the mucous membrane of the lesser curvature. The diagnosis was absence of rhythmic action of the gastro-enterostomy opening and slight chronic gastritis (superficial plus hypertrophic) of most portions of the stomach, but most marked in the area surrounding the opening.

Although the gastro-enterostomy stoma was situated in that part of the stomach most favorable for the development of the pylorus-like rhythm, none was present. Chronic gastritis of all portions of the stomach was present, which improved to a marked extent on dietary management. However, our past experience has shown that exacerbations frequently occur.

Case 36.—*History.*—A 59 year old man, seen on April 23, 1935, in 1930 had a cholecystectomy and gastro-enterostomy done (duodenal ulcer found). He was well for the following three years, but then attacks of dull pain developed in the right upper abdominal quadrant.

Physical Examination.—No significant findings were noted.

Roentgen Examination (April 25).—The gastro-enterostomy stoma was patent. There was localized tenderness at the region of the stoma.

Gastroscopy (April 25).—The entire stomach seemed to be distorted, and the orientation was difficult. The pylorus was not seen. A sickle-shaped fold was seen on the posterior wall which probably covered the gastro-enterostomy stoma. Toward the cardia the mucous membrane was velvet-like and swollen and contained many crevices. Toward the lower pole of the stomach there were also rather superficial circumscript changes; thick stripes of grayish mucus were seen. The mucous lake in the fornix was more transparent than usual and did not present its usual color. The diagnosis was circumscribed gastritis surrounding what was probably the funnel-shaped artificial opening. There were probably adhesions in the region of the pylorus and of the gastro-enterostomy stoma.

Three years after gastro-enterostomy was done abdominal distress again developed. There was no evidence of a recurrent ulcer. Gastroscopy revealed a circumscribed hypertrophic gastritis around the stoma. Perigastritic adhesions were also undoubtedly present.

Case 37.—*History.*—A 39 year old woman, seen on Nov. 28, 1934, had intermittent attacks of abdominal distress for eight years. In 1927 she underwent an operation for ulcer. After this she complained of a dull pressure pain in the epigastrium, which was more intense after meals. One week before the present examination severe diarrhea developed, followed by nausea and vomiting.

Physical Examination.—No significant findings were noted.

Laboratory Examination.—The gastric fluid after an Ewald test meal showed: free acid, 0; total acid, 12, and lactic acid, 3 plus. The stools were negative for blood.

Gastroscopy.—The action of the pylorus was normal. Just above the antrum the mucous membrane of the posterior wall showed no folds and appeared to be edematous. At a slightly higher level the gastro-enterostomy stoma was seen; there was no peristaltic contraction, and the Kerkring folds of the jejunum were marked. Numerous hemorrhages were seen on one fold of the lesser curvature. The other parts of the stomach were normal. The diagnosis was absence of peristalsis of the gastro-enterostomy stoma in the posterior wall; superficial gastritis of the lower parts of the posterior wall, and hemorrhages in one fold of the lesser curvature.

Superficial edematous gastritis is a common finding in the postoperative stomach in which the artificial opening is rigid. The finding of lactic acid without obstruction is frequent in such cases.

Gastritis After High Voltage Roentgen Therapy.—It is well known that roentgen treatment after the manner of Coutard for neoplastic lesions of the mouth causes a severe inflammation of the mucous membrane which heals after a certain length of time. The same observation has been made by one of us (R. S., in association with Dr. Sielmann) in cases of gastric neoplasm in which several of the patients were treated by the method of Coutard with excellent results.[16] The patients had not previously been operated on, so one may conclude that undoubtedly the severe inflammation was caused by the roentgen therapy. The gastritis following the Coutard treatment in case 12 occurred after resection had been done, so that it is not known to what extent this influenced the gastritis, but undoubtedly the major cause was the high voltage roentgen therapy. Gastroscopy was carried out thirteen days after the first treatment. On inspection the new opening was seen to be slitlike and to open rarely; it functioned with a rhythm peculiar to itself (fig. 13). The border of the opening was grayish yellow, and the mucous membrane of almost the entire stomach was red and swollen. In the lesser curvature there were linear areas of mucosal hemorrhages. Thick layers of dirty grayish mucus were observed on the posterior wall, thus making it impossible to state with certainty whether metastatic lesions were present. There was an extremely severe gastritis of almost the entire stomach, which was most probably due to the Coutard method of high voltage roentgen therapy.

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[16] Schindler, R., in discussion on Sielmann, H.: Erfahrungen mit der Röntgentiefenbestrahlung nach Coutard bei malignen Neubildungen, München. med. Wchnschr. **78**:384 (Feb. 27) 1931.

Unsatisfactorily Explained Cases.—In four cases (cases 38 to 41) only a part of the stomach was seen. For this reason we shall not report these cases other than to state briefly in what respects they were not satisfactory. In the first of them a peculiar crater was observed a few cubic centimeters from the edge of the gastro-enterostomy opening. A definite interpretation of this crater could not be made. Gastroscopy in the second case was done in the presence of a large audience; this disturbed the patient. Although chronic gastritis was found, the gastro-enterostomy opening could not be seen with certainty. In the third case an erosive gastritis was demonstrated, but here again the artificial opening could not be seen; furthermore, an unusual protrusion of the antrum could not be explained satisfactorily. In the final case gastritis was also demonstrated but an artificial opening was not disclosed.

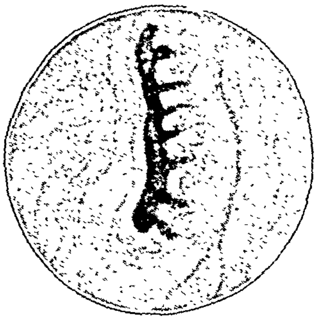

Fig. 13.—Gastroscopic picture of a slitlike stoma after gastric resection because of carcinoma of the pylorus. This stoma had a rhythmic function like a real pylorus. Pylorus-like action of an artificial stoma after resection has not yet been described.

Conclusions.—Gastroscopy of the postoperative stomach is not easy, since the operation produces changes in the contour which makes orientation difficult. The results with the Schindler-Wolf flexible gastroscope, however, are much more accurate than were those with the rigid instrument in which a maximum of only 50 per cent of artificial openings could be seen. In our series gastroscopy was performed on a total of thirty postoperative stomachs, on twelve after resection and on eighteen after gastro-enterostomy. The artificial opening was well observed in every stomach on which resection had been done. The gastro-enterostomy stoma was not demonstrated in three cases, or 10 per cent of all our postoperative cases. In two instances the opening was partially obscured by large folds.

Postoperative stomachs should be divided into two groups: those with a rhythmically working stoma and those with what we designate as a "patent stoma," by which we mean complete absence of activity at the opening, even though peristalsis in the intestine beyond the stoma is observed. The pylorus-like rhythm which develops in certain instances is an interesting and important phenomenon. Although it does not prevent the formation of recurrent ulcers, it does seem to prevent the development of chronic gastritis, which unfortunately is such a frequent postoperative occurrence and one which makes the operative result not wholly satisfactory. We observed this pylorus-like rhythm in four cases, twice in stomachs after resection and twice in stomachs after gastro-enterostomy. Functional adaptation thus took place in 13.3 per cent of all the postoperative stomachs which we observed, but we feel certain that it actually develops in a much higher percentage since gastritis does not develop, or at least infrequently, and hence the patient is not likely to present himself at the clinic. From the past experience of one of us (R. S.), we believe that this adaptation is probably more likely to occur after gastro-enterostomy than after resection, although we have no definite proof of this. At least gastro-enterostomy has the advantage that the stoma may be closed. More work should be done in respect to this entire problem by following the postoperative stomach gastroscopically.

It seems evident after gastroscopic study that the activity of the pylorus and the artificial stoma is not governed by a joint nervous center, since we have seen two cases in which both openings were observed in the same visual field and the rhythms were different. When the new stoma acquires this functional adaptation it presents the same stellar appearance when closed as has been described in respect to the pylorus. The higher centers may have some control over the pyloric activity, but the actual control of the rhythm probably lies in a center located in the wall of the stomach itself.

The patent opening often permits visualization of both loops of the intestine. The margin of the stoma may be stiff and even nodular as a result of operation; these nodes and postoperative pouches are frequent, and the nodes may be so large as to be mistaken for real tumors.

In our statistics of all gastroscopies done at the Billings Hospital we found 20 per cent of the stomachs normal, whereas among the thirty postoperative cases only three, or 10 per cent, appeared to be without significant lesions.

Recurrent ulcers were found in one case in which a rhythmically working gastro-enterostomy stoma was visualized. In this case six ulcers were found lying on the posterior wall close to the pylorus; only one of them was seen with certainty by roentgen examination. They all healed rapidly under medical management. No gastritis was observed at any time, but later small hemorrhages and one typical hemorrhagic erosion were seen. We believe such changes are frequently found in the ulcer type of stomach.

One jejunal ulcer was missed by gastroscopy; it was also not seen by roentgen examination. In one case the course of a jejunal ulcer was followed by a series of ten gastroscopic examinations; the ulcer was situated in the interior of the jejunum and was accompanied by severe gastrojejunitis. It healed completely under the Winkelstein method of treatment.

A large marginal ulcer of the stoma was seen in one case in which black silk threads were found hanging free into the cavity of the stoma. It was impossible to say to just what extent, if any, these threads were responsible for the development of the ulcer. We do know, however, that silk threads which cut through the mucous membrane after operation may cause trouble if they are not soon expelled. They first cause an inflammation; later erosions develop from the resulting friction. For these reasons they should be removed by operation.

All gastroscopists and many surgeons (Clairmont[13]) agree that chronic gastritis is the most frequent and important postoperative disease. It is true that in some cases gastritis may be present before the operation; our cases have shown, however (especially case 19), that gastritis does develop after operations on stomachs in which it was definitely not present before. Postoperative gastritis presents the most severe pictures that one sees of this condition, and since almost every case includes all types of this inflammation (superficial, hypertrophic and atrophic), we see no reason for attempting any descriptive classification. Thus we will add a fourth group to the three types already mentioned which we shall call simply "gastritis of the postoperative stomach." We do not know the exact etiologic factors which are responsible for the development of postoperative gastritis, although there is evidence that the constant reflux of intestinal juices may cause and maintain the inflammation. This is shown by the fact that in those cases in which there are no postoperative difficulties we generally found a rhythmically functioning stoma (one exception, case 23), which by its closing prevents the reflux of intestinal contents. Of the four cases which we observed in which a rhythmically functioning stoma was present, in none was gastritis observed except one which was seen after high voltage roentgen therapy by the Coutard method, which always produces severe gastritis. In two of the cases the stomach was normal; in the remaining one there was no gastritis but recurrent ulcers, which later completely healed. There is no doubt that patients suffer from this postoperative gastritis at least as much as they do from jejunal or recurrent ulcers; furthermore, gastritis occurs much more frequently (sixteen cases in our material). In addition to this, all observers agree that severe hemorrhages frequently result from this condition; this was observed twice in our cases. The treatment of gastritis is difficult, and for this reason the important task of the surgeon is to prevent its development. We have already stated that we believe that gastritis rarely develops if a rhythmically functioning stoma results. In cases of resection we do not know how the surgeon can favor the development of this functional adaptation, but we agree with Moutier that if the gastro-enterostomy stoma is made in the posterior wall close to the pylorus it is much more likely to take place. We will add that the opening should be made not only near the pylorus, on the posterior wall, but also close to the greater curvature. Further investigations must be made concerning this important question, because only by the prevention of chronic gastritis can operations for ulcer be completely satisfactory. The rôle which perigastritic adhesions play as a cause of postoperative distress has not been explained by our observations. They were encountered three times, but in only one case was there not also an associated gastritis. It is questionable in this case whether the adhesions were responsible for the symptoms, although it is not impossible. If it seems quite certain that they are the cause of distress, it seems probable that they should be removed surgically, although we know that this operation is generally of no great value.

In this series of cases we did not observe any instances of carcinoma at the gastro-enterostomy stoma.

SUMMARY

This paper is based on the findings of seventy-eight gastroscopic examinations carried out on forty-one patients. Thirteen of the forty-one patients underwent gastroscopy preceding operation and two of the thirteen again after operation. The remaining twenty-eight patients were all examined postoperatively; seven of this group again underwent operation after gastroscopy, thus giving us a biopsic control in twenty cases.

Although the gastroscopic diagnosis was confirmed in every case in which we had biopsic control (twenty cases), it must nevertheless be admitted that negative findings in gastroscopy are not entirely conclusive.

The differential diagnosis between benign and malignant ulceration is not difficult to determine after a gastroscopic examination by one trained in this field; even in the very early stage biopsy is not necessary. The differentiation between benign and malignant obstruction is more difficult but also possible. Gastroscopic diagnosis was proved to be correct in each instance (seven cases). The gastroscopic picture is more characteristic than is that of the gross specimen because of the presence of the circulating blood.

The operability of carcinoma was best determined by gastroscopy (nine cases).

Special attention is called to the fact that operation for gastric carcinoma frequently results in cure of long duration, particularly in cases in which the diagnosis is made early. Early gastroscopy together with an early roentgenogram is able to reveal operable carcinoma. Gastroscopy has proved to be superior to roentgen examination in certain cases; theoretically, in other cases, roentgen examination should be superior. The two methods are not competitors; each supplements the other, and good cooperation between the gastroscopist and the roentgenologist is essential.

Early diagnosis of gastric carcinoma can be brought about if each patient over 35 years of age who suffers from anorexia or significant loss of weight and in whom no other explanation for the symptoms is found is immediately examined gastroscopically and roentgenographically. Patients with atrophic gastritis or a benign tumor should be watched carefully by both methods. An unfavorable diffusely infiltrating carcinoma of the body of the stomach should be recognized by gastroscopy and excluded from operation. Exploratory laparotomy should be done only in those relatively few cases in which the operability of the lesion is not definitely determined by gastroscopic examination. This will result in a greatly lowered surgical mortality and will thus help to dispel the prejudice which so many hold in respect to the surgical treatment of carcinoma. This should not only bring a greater number of patients with carcinoma to the operating table but also result in the observation of a greater percentage of cases in the early stage, since a distinction will be made in the minds of the public between the prognosis of early and late cancer.

The artificial stoma was seen with the flexible gastroscope in twelve stomachs after resection and in fifteen after gastro-enterostomy; it was not seen in only three stomachs in which gastro-enterostomy had been done, or 10 per cent of all the postoperative stomachs seen. The finding of the stoma, however, is not easy; the correct instrument must be chosen in respect to the peculiarities of the individual case.

A relatively normal stomach was seen in only three instances (10 per cent). Recurrent ulcer was found in one case and a jejunal ulcer in two cases (and probably missed in one); simple hemorrhagic erosions were observed twice. Silk sutures which had cut through the mucous membrane and were hanging free into the gastric cavity were observed three times. The most frequent disease of the postoperative stomach is chronic gastritis; it was observed in fifteen of our cases. Gastroscopic examination was unsatisfactory in four cases.

An artificial stoma (after resection or gastro-enterostomy) may remain patent or may acquire pylorus-like rhythmic activity. Four stomas of the latter type were seen: two after resection and two after gastro-enterostomy. It seems quite certain that this pylorus-like adaptation protects the stomach against the development of postoperative gastritis. Although we do not know what conditions favor this development after resection, it does seem that gastro-enterostomies which are carried out in the posterior wall near the pylorus and close to the greater curvature have a greater tendency to bring about this adaptation. Gastro-enterostomy has a further advantage in that the stoma may be closed if necessary. The activity of the gastro-enterostomy stoma in those cases in which a functional adaptation has developed is not timed in the same rhythm as is shown by the pylorus.

Silk sutures which have not been expelled into the cavity of the stomach several months after operation should be surgically removed since they irritate the mucous membrane, causing chronic gastritis with painful erosions, and may even play a part in the development of jejunal ulcers.

The observations presented in this paper do not explain the rôle played by adhesions in the development of postoperative distress.

High voltage roentgen therapy by the Coutard method causes severe gastritis in the postoperative stomach just as it does in other mucous membranes.

The illustrations in the color and figures 1, 3, 4, 5, 7, 8, 9 and 10 are from Schindler, Rudolf: Gastroscopy, Chicago, University of Chicago Press, 1937.

TRUE BRANCHIOGENIC CYST AND FISTULA OF THE NECK

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In an article on "Congenital Cysts and Fistulae of the Neck,"[1] published in the *Annals of Surgery* in 1932, I went into detail as to the embryologic development of the branchial apparatus and of the anlage of the thymus.

In July 1935 a boy 9 years of age was referred to me through the courtesy of Dr. Tumen, who had observed the child for a number of years. The boy was born with a small opening on the lateral side of his neck just in front of the sternocleidomastoid muscle and just below the angle of the mandible, on a level with the hyoid bone. It was first noticed when he was 5 months old, when it was an opening the size of a pinpoint. The mother stated that colorless matter came out. A swelling developed below the left ear, and when the boy was 18 months old the swelling was lanced by a physician. It subsided, and the wound closed. After this at intervals the swelling would recur and open by itself, and a discharge would come through the previous incision. Three or four times in the next few years it was necessary to lance the swelling. When the boy was 4 years old it recurred worse than before, and he was operated on by another surgeon, who tried to dissect out the tract. Apparently, from the description as given by the parents and Dr. Tumen, at this operation an opening was made into the trachea, and the operating surgeon believed that the tract was connected with the trachea. The wound finally healed, but the same sequence of events continued for the next five years, until the present time. Dr. Tumen injected dye into the fistulous opening, and, as shown by the accompanying roentgenograms, it went upward in the direction of the tonsillar fossa (fig. 1). In view of this picture and the history and the studies of Wenglowski, as published in my article in 1932, I made a preoperative diagnosis of probable lateral cyst and fistula of the neck, a remnant of the pharyngothymic duct, and I felt that on operation I would probably find the tract running upward toward the tonsillar fossa and entering the pharynx through the bed of the removed tonsil or close to the posterior pillar. From the studies of the embryology of the branchial apparatus and the pharyngothymic duct, I definitely felt that there was no connection between the tract and the trachea.

In July 1935 the boy was operated on, tribromethanol in amylene hydrate supplemented by a general anesthetic being used. The findings at the time of operation were exceedingly interesting. The fistulous opening was circumscribed, and the

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The case reported in this paper was presented before the New York Surgical Society, April 22, 1936.

[1] Meyer, Herbert Willy: Congenital Cysts and Fistulae of the Neck, Ann. Surg. **95**:226-248 (Feb.) 1932.

infiltrated tissue surrounding the fistulous tract was dissected free from the sternocleidomastoid and the platysma myoides muscle. As expected, it did not run toward the trachea. There was an infiltrated area, that passed upward and somewhat posteriorly toward the ear, but this could easily be dissected free, and it was found that the main portion of the tract, which was thick and dense, passed upward and somewhat inward into the jugular fossa, but then, to my surprise, instead of curving forward toward the pharynx and tonsillar fossa it curved upward and backward to the very apex of the jugular fossa. The tract was firmly and densely adherent to the tip of the styloid process. As a matter of fact, it was a part of the styloid process, and in order to effect complete removal of the tract it was necessary to bite off the tip of the styloid process (fig. 2 *A*). This permitted complete and radical removal of the entire congenital tract. With closure of the wound an uneventful recovery took place, and two years later there had been no recurrence of the previous trouble.

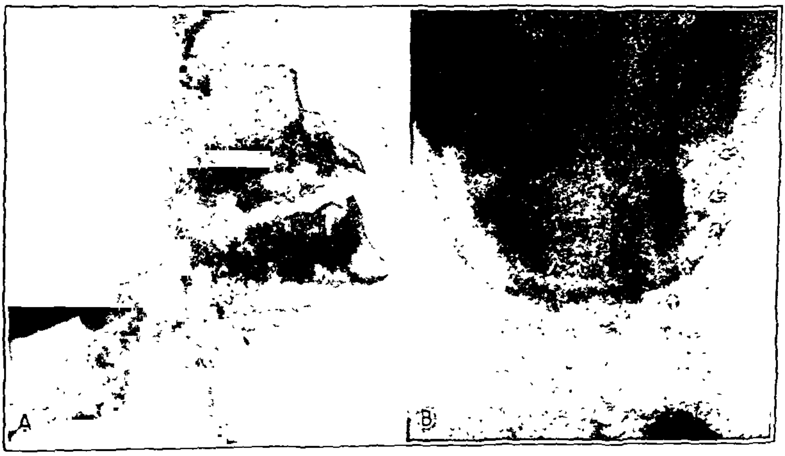

Fig. 1.—*A*, lateral roentgenogram showing the path taken by dye which was injected into the fistula. *B*, anteroposterior view. A tract is seen running upward toward the tonsillar fossa.

EMBRYOLOGY

A review of the embryology of this region was then made, and the facts as laid down by Wenglowski and as published by me in 1932 were again studied.

In an embryo of 6.5 mm. the first branchial arch goes to make up the upper jaw and the anterior portion of the lower jaw. The second arch goes to make up the operculum. The third and fourth arches do not meet in the middle. The first branchial cleft goes to form the external auditory canal. The second, third and fourth clefts are also visible. All of these branchial arches and clefts are covered with squamous epithelium.

The pharyngeal arches correspond to the branchial clefts. The first goes to make up the body of the tongue. The second, third and fourth arches are visible. The pharyngeal pouches correspond to the branchial arches. The first goes to make up the middle ear and the lobe of the ear, and the third, the anlage of the thymus.

In an embryo of 8 mm. the first branchial arch goes to make up the lips and the jaws. The second, third, fourth, fifth and sixth arches are visible. The branchial clefts are narrowed by the growth of the arches. The first cleft goes to make up the external auditory canal. Here the sinus cervicalis is deep and large.

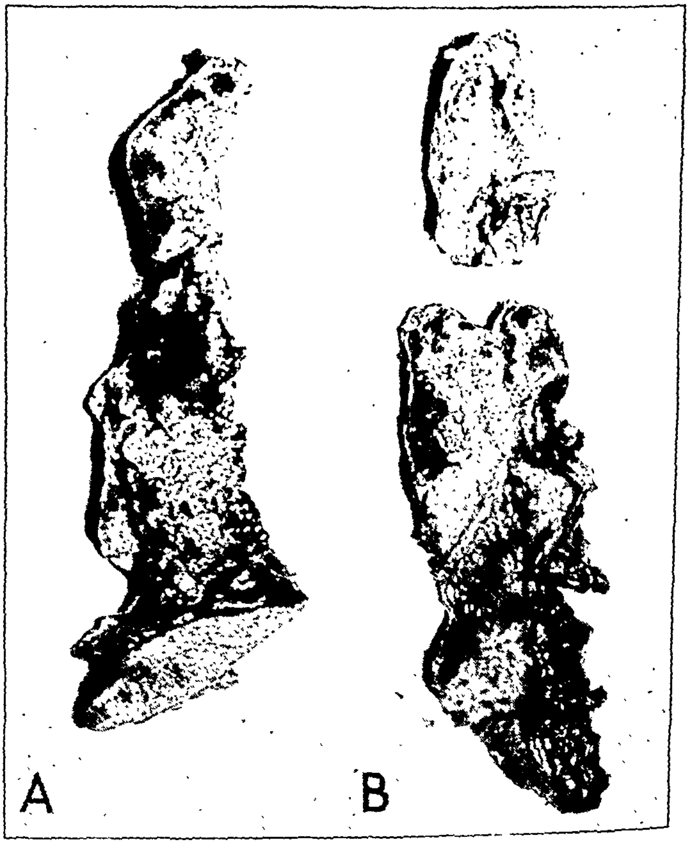

Fig. 2.—*A,* specimen removed at the time of radical excision, showing skin at the lower portion of the picture at the site of the external opening. A portion of the tip of the styloid process is at the uppermost portion of the photograph. *B,* the cyst laid open. Note the removal of skin with fine hairs in the upper section of the tract close to the styloid process.

The pharyngeal arches, one to four, go to make up the tongue. The pharyngeal pouches show the third to be the anlage of the thymus, while the fourth is the anlage of the lateral lobes of the thyroid. These pouches are covered by ciliated epithelium.

In an embryo of 11 mm. retrogression of the branchial apparatus takes place. The sinus cervicalis is closed from without, and only three arches are visible. The first branchial arch goes to make up the lower lip and the anlage of the jaw. The second branchial arch, which is conical, meets the opposite one in a narrow strand. The third branchial arch is not large and joins with the neck, displacing the entrance into the sinus cervicalis. The branchial clefts are becoming flat and narrow.

In embryos of 12 and 13 mm. further retrogression takes place. The first and second branchial arches are visible. The medial ends join with the neck, and the contour of the neck becomes visible.

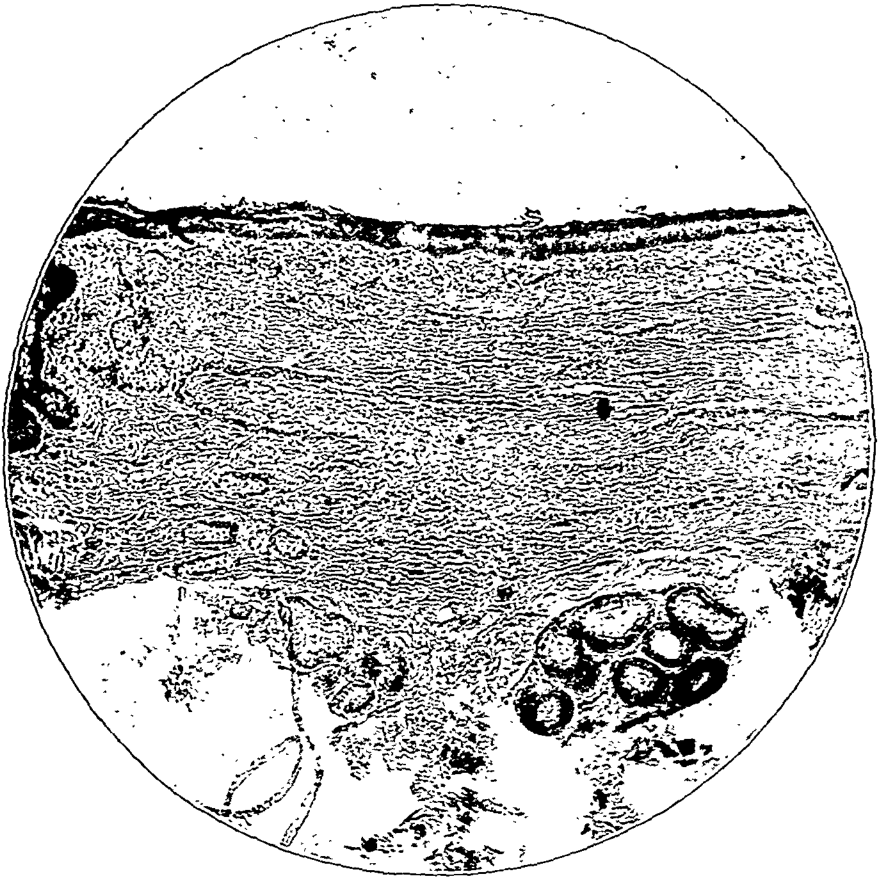

Fig. 3.—Section through the inner lining of the cyst close to the styloid process, showing sweat glands and normal epithelium.

COMMENT

The beginning of the branchial apparatus takes place in the second half of the first month of embryonic life. In the course of the second month the branchial apparatus completely disappears. In other words, it lasts only one month. According to Wenglowski, each branchial arch and cleft crosses the pharyngeal arch and pouch. His stated that the branchial arch coincides with the pharyngeal arch and the branchial cleft with the pharyngeal cleft. Wenglowski definitely disagreed with this.

The branchial apparatus runs forward, upward and orally, while the pharyngeal apparatus runs posterior, downward and aborally. The arches grow closer and closer, until the clefts disappear and the epithelium is displaced outward by the mesenchymal growth or by adhesion and obliteration.

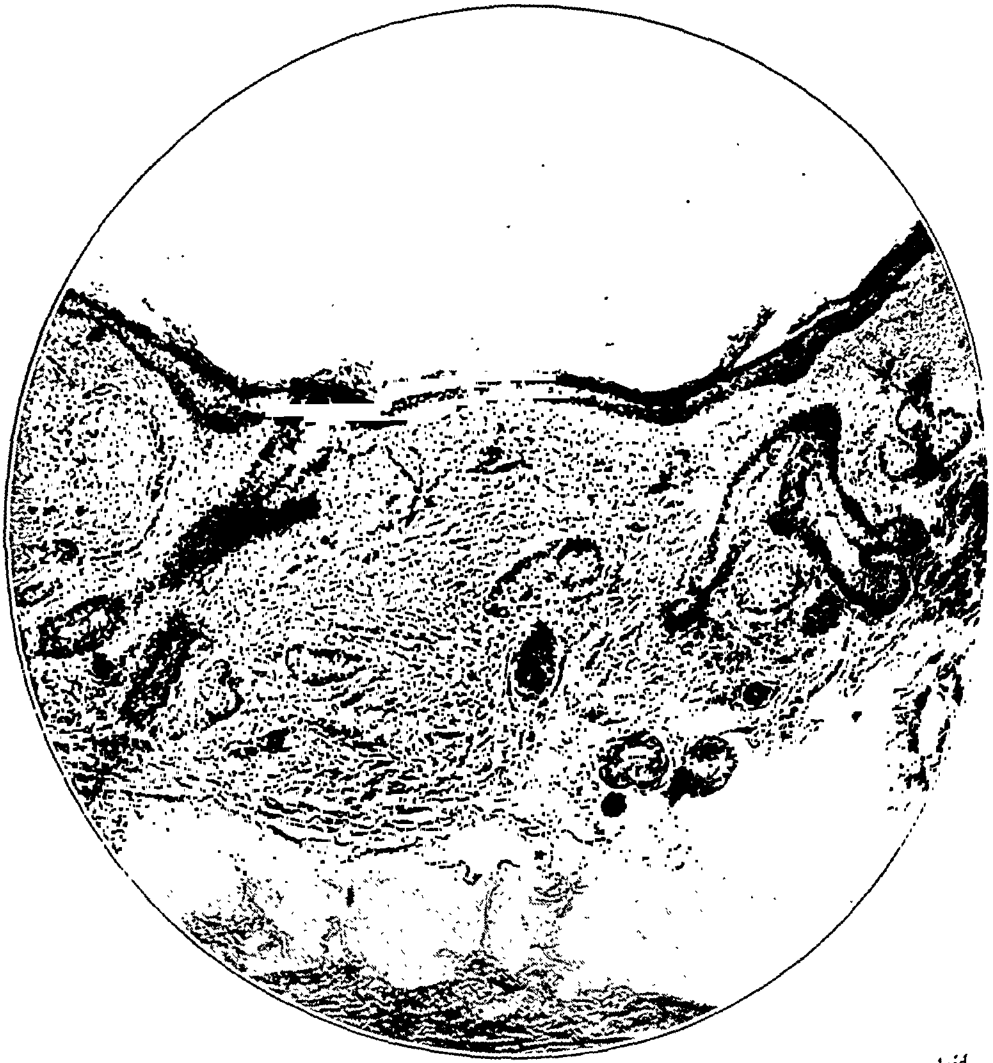

Fig. 4.—Section through the inner lining of the cyst close to the styloid process, showing hair follicles and sebaceous glands in the wall of the cyst.

In development the first arch goes to form the lateral portion of the upper lip and jaw, the lower lip and jaw and the body of the tongue. The second arch goes to make up the body of the hyoid, the stylohyoid ligament and muscle and the anterior portion of the base of the tongue and the arcus palatoglossus. The third arch goes to form the greater cornu of the hyoid bone, the posterior portion of the base of the tongue and the arcus palatopharyngeus. The fourth, fifth and sixth arches go to make up the soft parts of the neck surrounding the greater cornu of the hyoid bone.

The first cleft goes to make up the external auditory canal and the lobe of the ear; the second cleft, the tonsillar fossa; the third cleft, the thymus, and the fourth cleft, the lateral lobes of the thyroid.

The branchial apparatus belongs to the head and not to the neck. Any congenital pathologic condition referable to the branchial apparatus in human beings must rest along the lower jaw and around the hyoid bone and the cornu of this bone. Nothing below the lower level of the hyoid bone has any genetic relation with the branchial apparatus. All congenital anomalies caused by incomplete retrogression of the branchial apparatus must be located in the region around or above the lower border of the hyoid bone. Any congenital anomaly below this level is in definite relationship with the pharyngothymic duct and must be classified as a lateral cyst or fistula originating from the pharyngothymic duct.

In the case reported here, after the removal of the specimen the tract was opened and found to be lined with normal-looking skin and to be firmly attached to the styloid process (fig. 2 *B*). Microscopically, as shown in the photomicrographs, the wall of this tract contained all the appendages of the skin as hair follicles, sweat glands and sebaceous glands (figs. 3 and 4). In other words, the growth was a true branchiogenetic cyst and tract originating from the second branchial arch. Complete removal of this, of course, brought about a cure of the condition. It seems of interest to publish once more in résumé the embryology of this region, which is always interesting and fascinating. Any reader who is interested in a greater detail of these conditions is referred to the previous article by me which explains the aforementioned facts.[1]

LAXITY OF THE RADIO-ULNAR JOINT FOLLOWING COLLES' FRACTURE

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Since Sir Astley Cooper's [1] first description of the lesion in 1842, the literature has been replete with reports of frank dislocations at the lower radio-ulnar articulation associated with Colles' fracture. The more frequent but less severe degrees of relaxation in that joint, however, have received scant attention. In approximately one of every nine cases, Colles' fracture is followed after the healing period by laxity of the radio-ulnar joint. In some of these instances slight radio-ulnar diastasis is present, causing broadening of the wrist and apparent radial deviation of the hand. In others, the bones remain loosely in their normal position, and no deformity is apparent. In some cases the condition is entirely symptomless. In many, however, its association with lasting weakness, limitation of rotation and pain in the ulnar aspect of the wrist joint is of sufficient regularity to indicate a causal relationship which merits investigation.

Many observers have noted the persistence of these phenomena after Colles' fracture, but there has been little agreement about their interpretation or importance. In 1915 Darrach and Dwight [2] called attention to the severity and frequency of symptoms referable to the radio-ulnar joint following Colles' fracture, which they believed resulted from injury to the radio-ulnar ligaments. They maintained that with perfect reduction the normal relationship was regained and injury to the joint structures repaired. Additional support to the radio-ulnar joint, such as a leather wristlet, was advised after splinting, and in the event of persistent symptoms, subperiosteal resection of the head of the ulna was recommended. In 1917 Pilcher [3] wrote: "The projection of the end of the ulna on the inner anterior aspect of the wrist is the most noticeable and frequent permanent sequel of this fracture." Later, he added: "The [ulnar] projection may persist even when there is no appreciable deformity of the radius, through lack of full restoration of the close ligamentous bands that before the injury tied it to the radius." Pilcher, however, was not impressed by the "slight if any" symptoms, which follow this malposition. In 1921 Hitzrot and Murray[4] reviewed one hundred and ninety-six cases of Colles' fracture, noting the frequency of residual symptoms referable to the radio-ulnar joint. They did not attempt an explanation of these symptoms but reached the conclusion that functional disturbance is more marked in the more severe injuries and that early and complete anatomic restoration gives better functional results. On the basis of a review of the late results in four hundred and twenty-four cases of Colles' fracture, Edwards and Clayton[5] found that from two to four years after injury 23.1 per cent of the patients complained of some residual symptoms, among which pain or weakness on playing tennis or after heavy manual labor and tenderness over the internal lateral ligament were common. The symptoms were attributed to involvement of the radio-ulnar joint in the fracture, although roentgenographic evidence did not confirm this correlation. Grasby and Trick,[6] in a significant review of fifty cases in which fracture had been sustained from two to four years previously, found that when displacement was a marked feature the end-results were invariably unsatisfactory, owing to symptoms referable to the radio-ulnar joint. These workers concluded that the symptoms were due to arthritis at that joint secondary to incomplete reduction of the fracture. Bankart[7] agreed with their interpretation. The report of the Fracture Committee of the American College of Surgeons[8] mentioned the frequent prominence of the head of the ulna and pain referred to the region of the styloid process after healing of even a well reduced fracture. No suggestions regarding etiology or therapy were made. Moorhead[9] stated: "There is an inter-articular fibro-cartilage at the lower end of the radius, and if this is involved in the fracture, we are almost certain to have an eversion deformity despite anatomical setting of the bone itself." Ghormley[10] mentioned pain referable to the styloid process of the ulna as a troublesome complication following Colles' fracture but expressed the belief that it can be remedied by removal of the fractured styloid process of the ulna. Magnuson[11] considered the throwing out of alinement of the radio-ulnar joint and the tear or overstretching of its ligaments a serious source of disability unless "reduction is accomplished." Platt,[12] in a recent consideration of these disturbances of the inferior radio-ulnar articulation after Colles' fracture, wrote as follows:

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[1] Cooper, Astley: A Treatise on Dislocations and on Fractures of the Joints, ed. 2, London, J. Churchill, 1842, pp. 490, 496 and 497.

[2] Darrach, W., and Dwight, K.: Derangements of the Inferior Radio-Ulnar Articulation, M. Rec. **87**:708 (April 24) 1915.

[3] Pilcher, L. S.: Fractures of the Lower Extremity or Base of the Radius, Ann. Surg. **65**:1, 1917.

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[4] Hitzrot, J. M., and Murray, C. R.: The Factors That Influence Prognosis in Fractures at the Base of the Radius, Am. J. Surg. **35**:17, 1921.

[5] Edwards, H., and Clayton, E. B.: Fractures of the Lower End of the Radius in Adults, Brit. M. J. **1**:61 (Jan. 12) 1929.

[6] Grasby, E. D., and Trick, S. R.: *Investigation of the End-Results of* Colles' Fractures, Brit. M. J. **1**:391 (March 2) 1929.

[7] Bankart, A. S. B.: Treatment of Colles' Fracture, Brit. M. J. **1**:491 (March 16) 1929.

[8] American College of Surgeons Fracture Committee: Principles and Outline of Fracture Treatment, Bull. Am. Coll. Surgeons **15**:3, 1931.

[9] Moorhead, J. J.: Traumatotherapy: The Treatment of the Injured, Philadelphia, W. B. Saunders Company, 1931.

[10] Ghormley, R. K., and Mroz, R. J.: Fractures of the Wrist, Surg., Gynec. & Obst. **55**:377, 1932.

> In not less than fifty per cent of Colles' fractures, the fracture line on its mesial aspect reaches the upper limit of the articular facet for the head of the ulna, or enters the joint lower down. I have not been able to satisfy myself that involvement of the radio-ulnar joint in this fashion materially affects the function of rotation of the forearm, provided the injured joint is mobilized with discretion. Much more serious, however, is the disturbance which may result from a fracture of the ulnar styloid process at its base, or the equivalent injury—detachment of the fibro-cartilage from the lower end of the ulna. As regards the frequency of this latter complication, I have no statistical data, for clinical proof of its existence is rarely forthcoming. This point in the anatomy of Colles' fracture has exercised the minds of surgeons for many generations.

Scudder,[13] Key and Conwell,[14] Preston[15] and a few others called attention to widening of the distal radio-ulnar joint after Colles' fracture and suggested that symptoms referable to the joint are liable to ensue unless the displacement is reduced. In many other comprehensive texts and reviews no mention is made of the complication or its sequelae.

This brief survey of the recent literature suffices to point out that in the experience of many observers symptoms referable to the radio-ulnar joint and deviations of the ulna are not uncommon sequelae of Colles' fracture, particularly when displacement has been severe and reduction incomplete. That some have laid less emphasis on these complications is readily understandable when their divergent sources of material are considered—a divergence sufficient to account for variation of from less than 10 per cent to more than 70 per cent in the occurrence of coincident avulsion of the styloid process of the ulna.

In these studies the symptoms have been attributed to a wide range of disturbances of the radio-ulnar joint; to malalinement of the joint surfaces, to direct involvement of the joint in the fracture line, to arthritis, to rupture of the articular disk, to fracture of the styloid process of the ulna, to sprain of the ligaments of the radio-ulnar joint and, vaguely, to residual malposition.

On careful scrutiny, many of these hypotheses are untenable. Persistent symptoms referable to the radio-ulnar joint and pain on the ulnar aspect of the wrist have been observed with and without fracture of the styloid process of the ulna and, often, in the complete absence of stiffness of the finger and wrist joints or other arthritic manifestations. Roentgenograms have shown that direct involvement of the articular surface of the radio-ulnar joint in the fracture line can account for but a small proportion of these cases (Hitzrot and Murray and Edwards and Clayton). The greater frequency with which pain in the radio-ulnar joint occurs after incomplete reduction of a fracture has led some to infer that the pain was in some way directly referable to the residual displacement and could have been avoided by more perfect reduction. It is impossible to reconcile their conclusions with the fact that symptoms referable to the radio-ulnar joint, though less frequent, are often observed after faultless reposition and are absent in many striking cases of malposition.

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[11] Magnuson, Paul B.: Fractures, Philadelphia, J. B. Lippincott Company, 1933.

[12] Platt, H.: Colles' Fracture, Surg., Gynec. & Obst. **60**:542, 1935.

[13] Scudder, C. L.: Treatment of Fractures, Philadelphia, W. B. Saunders Company, 1931.

[14] Key, J. A., and Conwell, H. E.: The Management of Fractures, Dislocations, and Sprains, St. Louis, C. V. Mosby Company, 1934.

[15] Preston, M. E.: Fractures and Dislocations, St. Louis, C. V. Mosby Company, 1915.

It appears more reasonable, therefore, to regard the symptoms as due to a lesion of the distal radio-ulnar structures caused by displacement of the base of the radius at the time of injury, a lesion which sometimes, though not always, heals after perfect reposition of the bony fragment. The less frequent occurrence of symptoms referable to the radio-ulnar joint in cases of well reduced fracture is accounted for by the inclusion in this number of many cases in which the original bony displacement was insufficient to cause injury to the radio-ulnar ligaments as well as by occasional healing of these structures when the bone is well reduced.

In further support of this contention is the fact that in my own experience there is only one objective finding which has almost invariably characterized this condition, i. e., loss of stability at the distal radio-ulnar joint. In my opinion, this association and the foregoing findings show clearly the essential dependence of the symptoms on damage to the radio-ulnar ligaments sustained by the original trauma and indicate that even perfect reduction of the fracture cannot by itself be relied on to restore the stability of the radio-ulnar joint completely once the ligaments of this joint have been severely damaged.

The following studies were undertaken with the hope of clarifying the concept of the mechanism, prophylaxis and therapy of this condition.

ANATOMY

The articular surfaces composing the inferior radio-ulnar articulation are maintained in normal relationship by three ligamentous structures, the dorsal and ventral radio-ulnar ligaments and the triangular fibrocartilage or articular disk. The dorsal ligament is a weak structure reenforcing the dorsal joint capsule. It stretches from the posterior margin of the articular notch of the radius to the posterior surface of the head of the ulna. The ventral ligament is a similar mechanism extending between corresponding surfaces on the ventral aspect. The articular disk is a triangular band of fibrocartilage, the base of which is attached to the lower margin of the articular notch of the radius. Its apex attaches to a short ligament, which in turn inserts into the base and the inner surface of the styloid process of the ulna and the internal lateral ligament (fig. 1).

This mechanism is so adjusted that in most persons motion is entirely limited to the gliding of the sigmoid cavity of the radius about the articular surface of the head of the ulna. Occasionally, a slight and symptomless degree of laxity is present. Stability of the distal radio-ulnar joint is maintained in all rotary positions of the forearm by variation in the tension of these ligaments. The dorsal radio-ulnar ligament is spanned in pronation and relaxed in supination. The ventral radio-ulnar ligament is relaxed in pronation and tensed in supination. The articular disk is fairly taut in all rotary positions, its anterior fibers tightening in supination and its posterior fibers, in pronation. In pronation, then, the stability of the joint is maintained by the dorsal radio-ulnar ligament and the articular disk, and since Colles' fracture is practically always sustained with the forearm prone, these ligaments which are tensed in that position are the ones jeopardized by displacement of the radial fragment (fig. 2).

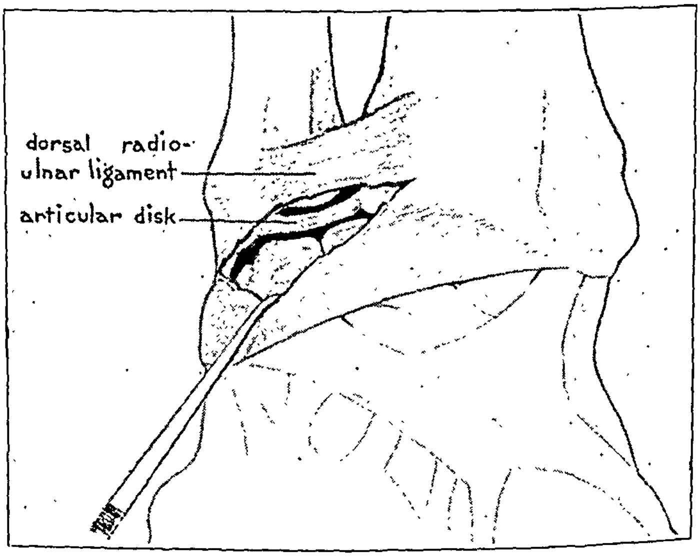

Fig. 1.—Diagram showing the radio-ulnar ligament and articular disk.

Anatomically, the articular disk is more vulnerable than the dorsal radio-ulnar ligament. The broad, firm fixation of its base to the base of the radius prevents any considerable degree of forward and backward sliding. It cannot be displaced upward because the head of the ulna is directly above. Moreover, it is located where the greatest radio-ulnar diastasis exists when the radial fragment is angulated and displaced upward. For these reasons, anything more than minimal upward and backward displacement of this fragment cannot occur without producing at least a partial tear of this structure (or its equivalent, avulsion of the styloid process of the ulna).

The dorsal radio-ulnar ligament appears to be better protected. If the arm is not in pronation at the time of fracture, this ligament is relaxed and so may escape injury. The height of its upper radial attachment is subject to considerable normal variation but is seldom less than ¾ inch (1.9 cm.) above the highest point of the wrist joint. This level is higher than that at which Colles' fracture occurs in most instances, and for this reason a good portion of the ligament may remain attached to the shaft and so be preserved from injury when the distal fragment is displaced. The structure is not strong, and rupture of its fibers is anatomically possible, even in a low fracture, if the ligament is tightly spanned by pronation of the forearm (*fig.* 3).

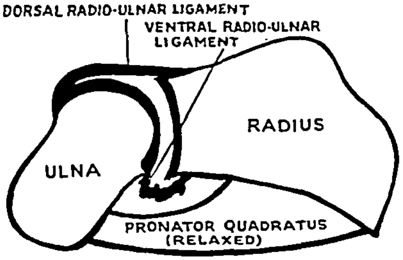
DORSAL RADIO-ULNAR LIGAMENT
VENTRAL RADIO-ULNAR LIGAMENT
RADIUS
ULNA
PRONATOR QUADRATUS (RELAXED)

Fig. 2.—Diagrammatic cross-section of the distal radio-ulnar joint in pronation, showing tension of the dorsal radio-ulnar ligament and relaxation of the ventral radio-ulnar ligament.

EXPERIMENTS ON CADAVERS

With these facts in mind, experiments on cadavers were undertaken to determine the relative importance of the articular disk and the dorsal radio-ulnar ligament in the maintenance of fixation of the distal radio-ulnar joint.

(*a*) In the forearm of a cadaver the insertion of the articular disk into the styloid process of the ulna was severed with a tenotome. A minimal degree of laxity of the radio-ulnar joint in the prone position and a slightly greater degree in the midposition followed this operation. The lower half of the dorsal radio-ulnar ligament was then cut with the forearm in pronation. The lower end of the ulna could now be freely moved up and down with reference to the rest of the forearm. Complete sections of the dorsal radio-ulnar ligament permitted a still greater range of motion, and with the arm in pronation it was now possible to dislocate the lower end of the ulna completely. In supination the tension of the ventral ligament returned the ulna to its normal position and held it firmly there. This experiment was repeated in two other forearms with identical results.

(*b*) In each of three forearms the dorsal radio-ulnar ligament was sectioned and the articular disk permitted to remain intact. In all cases this produced moderate laxity at the radio-ulnar joint in the prone position. When the forearm was in full supination, the edges of the tear in the dorsal radio-ulnar ligament were approximated, and complete stability was restored.

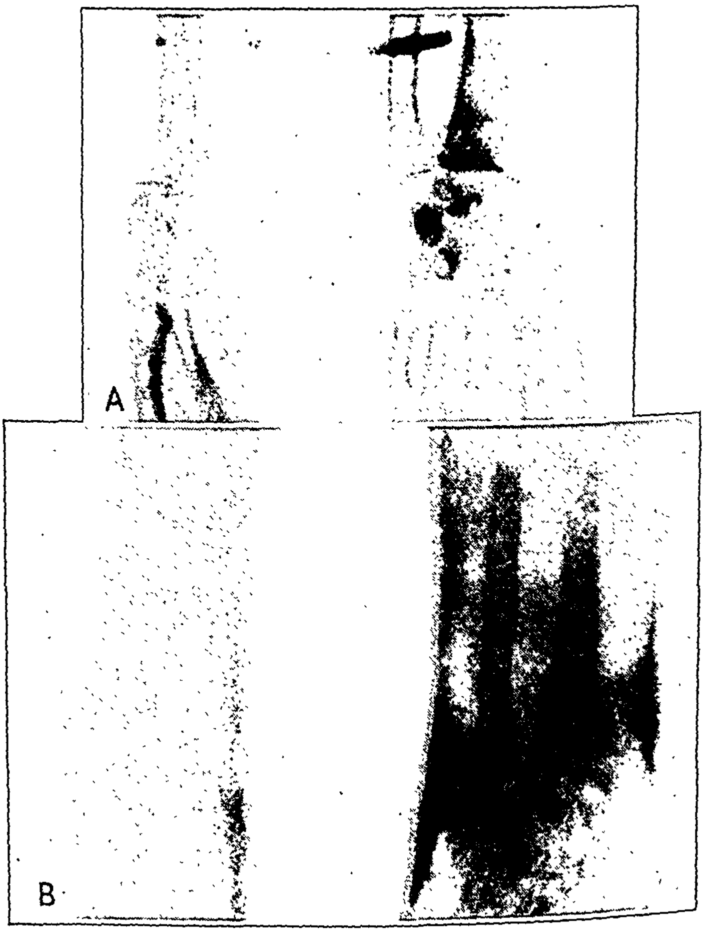

Fig. 3 (M. B.).—*A*, roentgenogram illustrating a high type of Colles' fracture which jeopardizes radio-ulnar ligaments. The radio-ulnar joint is not involved in the fracture line. *B*, roentgenogram showing perfect bony reduction, in spite of which symptoms referable to the radio-ulnar joint have persisted for over one year.

These findings may be summarized as follows:

1. With the forearm prone, section of the articular disk alone results in minimal laxity of the radio-ulnar joint.

2. With the forearm prone, section of the dorsal radio-ulnar ligament results in moderate laxity. (As the articular disk is more vul-

nerable than the dorsal radio-ulnar ligament, this condition must be clinically rare.)

3. Section of the articular disk plus partial section of the dorsal radio-ulnar ligament increases the degree of laxity of the radio-ulnar joint.

4. Complete section (of both the articular disk and the radio-ulnar ligament) permits great freedom of motion between the distal end of the radius and the ulna, so that in pronation complete dorsal dislocation of the head of the ulna is possible.

5. The position of supination reduces any displacement of the ulna and approximates the torn edges of the dorsal radio-ulnar ligament.

These findings justify certain clinical inferences which clarify the concept of the lesion. Primarily, since the degree of laxity of the radio-ulnar joint after Colles' fracture is considerably greater in most cases than that elicited by section of the articular disk alone, it may be safely assumed that in these cases the integrity of the dorsal radio-ulnar ligament is also compromised. Complete avulsion of the dorsal radio-ulnar ligament is not necessary to produce a moderate degree of laxity, and it is likely that in most cases a partial tear or sprain in this ligament plus a partial or complete avulsion of the articular disk or the styloid process of the ulna constitutes the pathologic basis for laxity after Colles' fractures.

On this basis may be explained the absence of perceptible laxity of the radio-ulnar joint in many cases of Colles' fracture in which the styloid process of the ulna is avulsed at the base and consequent complete loss of function of the articular disk must occur. Although the styloid process of the ulna is fractured in well over half of all cases of Colles' fracture, preservation of the dorsal radio-ulnar ligament suffices to retain stability of the radio-ulnar joint. Dissections on cadavers have indicated that the dorsal radio-ulnar ligament may be preserved if the fracture is low or if displacement is minimal, and, clinically, fractures with these characteristics are seldom complicated by laxity or its attendant symptoms.

Of greater practical importance is the freedom of motion permitted by the intact ventral radio-ulnar ligament in the prone position after the dorsal radio-ulnar ligament and articular disk are sectioned. This laxity of the ventral ligament in pronation accounts for its preservation in all but the most extensive Colles' fracture-displacements, a circumstance which permits its utilization in practically all cases to restore the integrity of the radio-ulnar joint. The supine position, by spanning this ligament, draws the head of the radius and of the ulna together. In this position the pronator quadratus muscle is also stretched, so that it can actively assist in this function. Moreover, supination relaxes both the dorsal radio-ulnar ligament and the posterior portion of the articular disk, so that any torn edges may be approximated, and healing may occur without distortion. These observations clearly indicate that from an anatomic standpoint supination is the position of choice for the treatment of injury of the radio-ulnar ligament accompanying Colles' fracture.

SYMPTOMS

Laxity of the radio-ulnar joint may be entirely asymptomatic or may be the cause of severe disability. When pain is present, it ranges from a dull ache on the ulnar aspect of the wrist accompanying and following function to recurrent acute paralyzing twinges. Pain of the latter character is particularly associated with pronation against resistance, and its severity is sometimes such that any object in the hand is immediately dropped. Usually these pains are most severe during the first few months of convalescence, after which their intensity diminishes to a less severe but constant level. On the other hand, pain sometimes increases with the resumption of full activity, so that it becomes most troublesome four or five months after the time of fracture.

On examination the wrist joint may appear slightly broadened owing to mesial displacement of the head of the ulna. In other instances the ulna remains loosely in its normal position, so that no deformity is apparent. Tenderness over the dorsal radio-ulnar ligament, below and on the lateral aspect of the wrist joint, is usually present. Limitation of flexion and extension at the wrist and fingers is not referable to laxity of the radio-ulnar joint. Supination is usually limited, but both active and passive pronation cause severe pain at its limit. In cases of recent fracture all of these objective findings are obscured by the proximity of the fracture hematoma and reaction. Slight radio-ulnar diastasis may or may not be visualized by roentgenographic examination, and it must be emphasized that films cannot be relied on for diagnosis of this condition.

Immediately after reduction of the bony displacement or at any time thereafter the condition may be recognized with ease if the radio-ulnar joint is examined for stability, but only by this procedure. One hand of the examiner fixes the radius and hand of the patient firmly in pronation so that no rotation is possible. With the thumb and forefinger of the other hand, the head of the ulna is gripped, and an effort is made to displace it upward and downward. The degree of free motion so elicited may be compared with that in the opposite wrist as a control.

The disability caused by laxity of the radio-ulnar joint is exceedingly difficult to evaluate. No definite standards of efficiency can be employed when the demands of the patient's occupation on the function of the wrist are at such wide variance. Moreover, a lesion of the right wrist generally causes much greater disability than a similar left-sided lesion, a fact which is not accorded due consideration in the evaluation of the results of Colles' fracture. As most of the patients with this type of fracture are able to resume their former occupations more or less well, the disability in most instances is considered as relatively minor. However, within the past year, the following typical complaints were received. One carpenter was able to perform his usual functions fairly well, except for complete inability to use a screw-driver because of pain. Two tennis players were compelled to abandon the game because of severe pain at every powerful stroke. A middle-aged woman complained of severe pain on the ulnar aspect of the joint, weakness and swelling after sewing or knitting for a short time. Two other women suffered similarly after a few hours of household duties. These illustrative complaints were chosen from patients whose injuries had been sustained at least eight months previously. While other findings in these cases were variable, the radio-ulnar joint in all instances was unstable and, with the wrist prone, the head of the ulna could be freely moved with reference to the base of the radius.

PROPHYLAXIS

Complete reduction of a fracture is of maximal importance for restoring the normal relationship of the distal radio-ulnar joint and constitutes the first step in the prevention of permanent laxity of the joint. Evidence from all sources indicates the greater frequency with which symptoms follow incomplete reductions. The greater severity of symptoms in the incompletely reduced fractures is illustrated in the appended table.

Directly after the accomplishment of reduction, the radio-ulnar joint should be tested for stability. If stability is present at this examination, subsequent laxity need not be feared, and the customary forearm splint suffices for immobilization. If instability is discovered, the forearm should be rotated into full supination and maintained in that position by inclusion of the upper part of the arm in the immobilizing device for a period of from three to four weeks. The position of supination, by tensing the ventral radio-ulnar ligament and spanning the pronator quadratus muscle, draws the muscles of the radius and ulna together. It relaxes the dorsal radio-ulnar ligament and posterior fibers of the articular disk, so that torn edges may be approximated during the process of healing.

If the arm is not fixed in supination but is permitted to rotate after reduction, it has a tendency to fall into pronation. The dorsal radio-ulnar ligament is thus subjected to continuous or intermittent tension, and healing with elongation must be anticipated.

It is interesting that with the wrist in supination the displacement of an avulsed styloid process of the ulna is reduced (fig. 4), and if

Data on Symptoms Referable to the Radio-Ulnar Joint After Colles' Fracture

				Original Fracture Data					Present Status	Objective Findings			
Patient	Age	Sex	Arm	Displacement	Level	Styloid Process of Ulna	Reduction	Duration	Persistent Symptoms	Arthritis	Broadening of Wrist	Pain on Pronation	Radio-Ulnar Laxity
H. S.	24	F	L	?	High	—	Excellent	6½ yr.	Wrist weak since fracture; pain became severe when nursing commenced one year ago; since then constant pain during working hours on ulnar aspect and over radio-ulnar joint	....	Slight	Slight	+
L. R.	28	M	R	Marked	High	+	Good	3¼ yr.	Patient unable to play tennis since onset because of acute sharp twinges of pain; occasional pains at other times but not severe; persistent weakness	....	....	Very slight	+
M. L.	71	F	R	?	Medium	—	Poor	3 yr.	Arthritic pains and limitation of wrist and finger motion severe for 4 months after fracture; since then, localization at radio-ulnar joint and ulnar aspect; unable to sew or knit	+ Fingers and wrist	Marked	Severe	+
B. T.	47	F	R	Moderate	High	+	Fair; ⅛ inch (0.3 cm.) radial shortening	2½ yr.	Result satisfactory but for weakness and pain after working (housework); condition has persisted without change for 2 years	....	Slight	Severe	+
B. R.	52	F	L	Marked	High	+	Poor; ¼ inch (0.6 cm.) radial shortening	2 yr.	Very severe pain over radio-ulnar joint and ulnar aspect of wrist—constant and with acute twinges unless complete rest is observed; unable to sew for 5 minutes	+ Slight; wrist	Marked	Severe	++
C. B.	35	M	R	Marked	High	—	Excellent	2 yr.	Slight weakness; repeated acute twinges of paralyzing pain of increasing frequency at any motion of twisting against resistance	....	....	Very slight	+
B. P.	51	M	R	Marked	High	—	Good	1¼ yr.	Working as carpenter but has pain when he has to use tools requiring a twisting motion; pain is chiefly on ulnar aspect of wrist	....	Slight	Moderate	+
M. S.	31	M	R	Marked	Medium	+	Fair; ⅛ inch radial shortening	1 yr.	Persistent weakness; sudden acute pains at radio-ulnar joint on athletic activity	....	....	....	+
N. C.	36	F	R	Moderate	High	+	Poor; ⅛ inch radial shortening	9 mo.	Pains of moderate severity on working and for several hours thereafter; no acute twinges; disability not great; pain most severe over radio-ulnar joint	....	Slight	Severe	+

sufficient time is given, it may reunite with the shaft so that complete restitutio ad integrum of the joint is established. Practically, it has not been deemed advisable to maintain supination long enough to permit such bony union to occur.

In certain instances Colles' fracture cannot be completely reduced owing to telescoping of the bony structure of the head of the radius. As in cases in which the fracture is well reduced, when the fracture is unassociated with laxity of the radio-ulnar joint its late occurrence need not be feared, and the employment of the supinated position is unnecessary. Those fractures which, for this or other reasons, have not been well reduced and manifest laxity of the radio-ulnar joint constitute the greatest source of late symptoms referable to this joint. Upward displacement of the base of the radius in such fractures entails equivalent displacement of the fragment of dorsal radio-ulnar ligament attached. The resulting separation of the ligament's torn edges precludes healing, a fact which probably accounts for the frequency of late symptoms referable to the radio-ulnar joint. Approximation of the torn structure can be attained only by assumption of the supinated position.

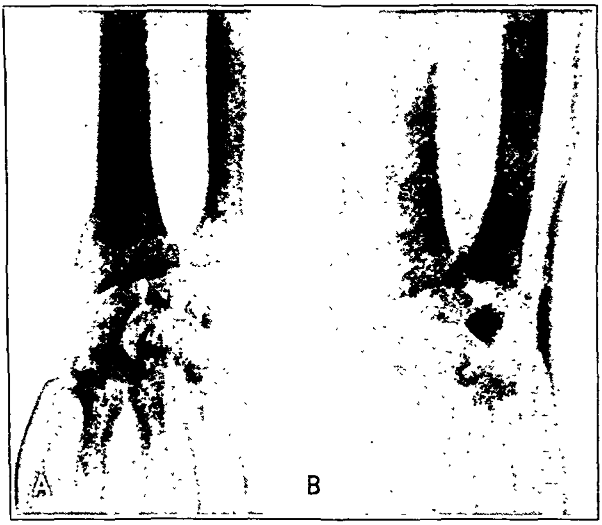

Fig. 4.—*A*, a roentgenogram showing reduction of Colles' fracture in pronation, and *B*, one showing reduction of the displaced styloid process of the ulna after immobilization in supination.

Two theoretical objections to the employment of supination in the treatment of Colles' fracture merit consideration. The desirability of limiting rotational movement for several weeks in persons with arthritis is questionable. It is my opinion that in such cases the relative advantages of permanent relaxation of the radio-ulnar joint as opposed to prolonged stiffness of the joint must be individually evaluated. It has been suggested that the reduction of the fracture attained with the arm in pronation might be jeopardized by subsequent rotation into supination. To determine whether such slipping might occur, ten fractures were checked by roentgenograms after reduction and again after supination. In no instance had supination affected the position of the bony fragment.

Although the recovery of full active rotation is somewhat delayed by fixation in supination, stability of the radio-ulnar joint is present when the splints are removed, and the danger of permanent pain or deformity from this source has been avoided.

In the past two years the foregoing technic has been employed on twelve cases of Colles' fracture in which, after reduction, there was laxity of the radio-ulnar joint. Immediately on removal of the fixation from the upper part of the arm, five of the patients were able to rotate the hand freely and without pain. In the remainder, the return of free rotation was delayed from one to three weeks. Except in one case (that of a severely comminuted fracture in which it seemed that rupture of both ventral and dorsal ligaments had occurred) stability was present when the plaster was removed. In these eleven cases the joints have remained stable and painless. Although a detailed report on the end-results must be deferred for several years, at the present time it can be definitely stated that in these patients instability of the radio-ulnar joint has been prevented, prominence of the head of the ulna has been greatly minimized and freedom from symptoms referable to the radio-ulnar joint has been complete.

THERAPY

The treatment of laxity of the radio-ulnar joint is determined by the duration, the course and the severity of the symptoms. When the wrist is painful only during and after certain activities, a 2 inch (5 cm.) broad leather wristlet worn during these times can give considerable relief. That this device is not more effective may be attributable to the fact that the forearm measures slightly less in circumference when it is in pronation. As a consequence, the wristlet is more slack in that position in which its support is most necessary. An elastic wristlet has not sufficient strength to be of value.

Radical treatment is indicated when symptoms have continued for at least four months after injury and when, in spite of judicious conservative treatment, they have exhibited no tendency to subside. The following procedure has, in my experience, proved adequate when there is no gross bony distortion of either articular facet.

A dorsolateral incision 1½ inches (3.8 cm.) in length is made at the level of the radio-ulnar joint, and the dorsal radio-ulnar ligament is exposed. The ligament is usually found to be redundant and scarified. All scar tissue is excised, and, through this approach, the radio-ulnar joint surfaces are exposed. Any granulation tissue between the head of the ulna and the radius is then curetted out. If the triangular fibrocartilage is distorted or fractured, this structure or any part of it may be freely removed. It may be recalled that the experiments on cadavers showed only minimal laxity after section of this disk if the dorsal radio-ulnar ligament was intact. With the hand in pronation, the head of the ulna is pressed tightly against the sigmoid cavity of the radius, and the remaining dorsal radio-ulnar ligament and capsule are sewed

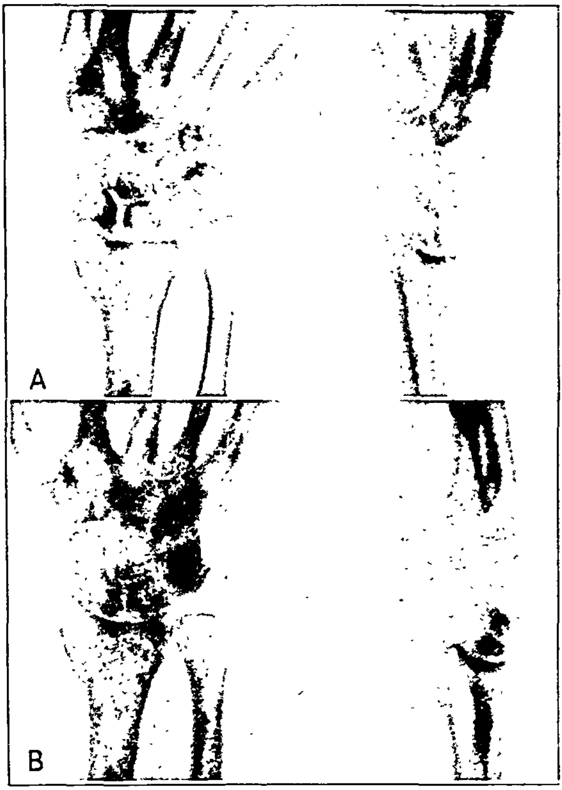

Fig. 5. (B. R.).—*A*, a roentgenogram taken after eight months of complete incapacitation following poor reduction of Colles' fracture. Motion of the fingers and extension of the wrist were full. Flexion was limited to 75 degrees and was slightly painful. Supination was limited but painless, and pronation was full but exquisitely painful. Tenderness was elicited over the head of the ulna, the styloid process of the ulna and the dorsal radio-ulnar ligament. There was free mobility of the ulna. *B*, a roentgenogram taken one month after suture of the ulna and excision of the styloid process of the ulna and the articular disk. All symptoms were gone except limitation of flexion.

firmly together with fine catgut. Sufficient ligamentous tissue is always available for this purpose, and enough may remain to plicate and reenforce the suture line. If the styloid process of the ulna is displaced, the incision in the skin may then be laterally retracted and the styloid process excised. In this event, a firm suture is inserted to anchor the internal lateral ligament to the base of the head of the ulna. The incision is then closed, and a light circular dressing is applied. Some function may be permitted at the end of a week and, as a rule, in from three to six weeks symptoms have completely disappeared (fig. 5).

Subperiosteal resection of the head of the ulna as recommended by Darrach and Dwight is a valuable procedure, but its employment should be limited to those cases in which there is gross bony distortion.

In case of doubt the joint surfaces can be exposed and inspected through the approach described. If resection is then considered advisable, the incision can be easily extended for this operation. As yet, I have not had occasion to resect.

SUMMARY AND CONCLUSIONS

Symptoms referable to the radio-ulnar joint and pain on the ulnar aspect of the wrist joint are a frequent source of incapacitation following Colles' fracture and are almost invariably found in association with laxity of the radio-ulnar joint.

Laxity of the radio-ulnar joint and its consequent symptoms often persist, even after perfect bony replacement.

Rupture of the articular disk alone does not produce sufficient laxity to account for this condition (experiment on a cadaver).

The laxity must be due to a sprain or tear of the dorsal radio-ulnar ligament plus partial or complete rupture of the articular disk or its equivalent, avulsion of the styloid process of the ulna (experiment on a cadaver).

Laxity of the radio-ulnar joint may be diagnosed by manual examination immediately after reduction of the fracture of the radius (roentgenographic evidence is unreliable).

In the event of this finding, the position of supination offers the best opportunity for these structures to heal without tension, so preventing residual laxity of the radio-ulnar joint.

Mild symptoms may be considerably relieved by a broad laced leather wristlet.

A simple operative procedure is presented for the cure of laxity of the radio-ulnar joint and its attendant symptoms, in which any residual displacement of the radial fragment is not disturbed.

TORSION OF THE PEDICLE IN OVARIAN TUMORS

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Torsion of the pedicle is a serious and most common complication of ovarian tumor. The treatment in all instances is surgical. Ninety-seven cases of torsion of the pedicle were found at 1,101 consecutive operations for ovarian tumor performed at the Mount Sinai Hospital between 1924 and 1935. The grave hazards of this condition, the pathologic changes and the symptoms are of particular interest and importance. There is a dearth of literature pertaining to the subject.

Percentage Incidence of Torsion of the Pedicle in Various Types of Ovarian Tumors

Type of Tumor	Series at Mount Sinai Hospital		Grotenfeldt's Series, Percentage	Frank's[1] Series, Percentage
	Number of Cases	Percentage		
Fibroma	7	29.0	29.0	21.0
Papillary serous cystadenoma	36	25.0	18.4	15.1
Dermoid cysts	33	17.5	17.2	8.3
Papillary pseudomucinous cystadenoma	8	13.0	....	....
Papillary pseudomucinous cystadenocarcinoma	1	9.0	....	....
Simple cysts	36	7.0	21.3	20.0
Papillary serous cystadenocarcinoma	3	2.0	....	....
Sarcoma	0	...	6.4	12.5
Carcinoma	0	...	4.0	2.7

The incidence of torsion in this series of ovarian tumors at Mount Sinai Hospital was 9 per cent. Eden and Lockyer found a frequency of 2 per cent; Frank,[1] 8.5 per cent, and Araya and Carbo, 10.22 per cent. S. Wiener reported 33 instances of torsion or a frequency of 12.26 per cent in his series of cases of ovarian tumor and Grotenfeldt, 83 instances, or a frequency of 15.2 per cent. The figures on the comparative incidence of torsion of the pedicle among various types of ovarian tumor are given in the accompanying table.

The solid and semisolid tumors show the greatest frequency of torsion. In the series of cases of ovarian tumor observed at the Mount Sinai Hospital there were 522 simple cysts, with torsion in only 7 per cent. This is at variance with the figures of Grotenfeldt and Frank.

From the Gynecological Service of Mount Sinai Hospital.

[1] Frank, R. T.: Gynecological and Obstetrical Pathology, ed. 2, New York, D. Appleton and Company, 1931.

CAUSE, EXTENT AND DIRECTION OF TORSION

The exact cause of twisting is not known. Factors favoring rotation are a smooth tumor surface, solidity, a tumor of moderate size, a roomy pelvis and a relaxed abdominal wall. Large growths are not prone to turn. A thin, long pedicle, acquired probably by traction, turns more readily than one which is short and thick. Infection and malignancy produce adhesions early, which immobilize the tumor.

It is noted in the table that solid and semisolid tumors rotate from two to four times more frequently than cystic ones. The relative frequency of torsion of the pedicle among solid fibromas (29 per cent) is not usually emphasized because of the rarity of this growth. Nevertheless, the *high incidence is significant.* Benign papillary, solid and semisolid tumors, for example, also show a much higher frequency of torsion than simple cysts, in spite of the fact that the former are more prone to adhesions from irritation, inflammation or local metastasis. The specific weight, therefore, may be a factor in favoring the rotation of ovarian tumors.

Rotation has been attributed to falls, sudden exercise, muscular effort or trauma.[2] It may be precipitated by contraction of the abdominal wall, straining, coughing and movement of the intestines and bladder, as well as micturition or defecation. The laxity of the abdominal wall after childbirth predisposes to twisting. Postpartum changes in intra-abdominal pressure, due to emptying of the uterus, may cause torsion suddenly, whereas constant, minute growth impulses covering a long period may effect rotation slowly (Frank). Torsion has been ascribed to fetal movements and change in uterine position, and it is thought that the unequal growth and weight of the different cystic areas may influence the condition.

The extent of the torsion may vary from one-half to fifteen turns of the pedicle. The greatest number of coils in this group of cases was seven. It is likely that emergence from the true pelvis rotates the tumor 90 degrees. Usually a complete twist suffices to produce some circulatory changes and symptoms. However, many turns of a long, thin pedicle may remain asymptomatic.

The single complete twist is the most frequent. It occurred in 36 of 96 cases, or 37 per cent. Partial turns varying from one-half to a complete rotation were found in 15 instances. One and a half, two and three twists occurred in 3 instances, respectively. There were 4 tumors with four pedicle turns in each case and single instances of five and seven rotations of the pedicle.

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[2] Graves, W. P.: Gynecology, ed. 3, Philadelphia, W. B. Saunders Company, 1923, pp. 446-447.

Occasionally the infundibulopelvic fold and the broad ligament, as well as the fallopian tube and the round ligament, are involved. There were 17 cases of twisted fallopian tubes, 8 instances of twisting of the infundibulopelvic ligaments and 1 case of twisting of the round ligament. Extreme torsion of the broad ligament occurred twice.

DIRECTION OF ROTATION AND SIZE OF CYST

According to Küstner's law, a tumor on the left side rotates from left to right and one on the right side rotates from right to left.[3] Eighty-five per cent of cases of torsion adhere to this rule (Pfannenstiel). The operative reports mentioning the direction of rotation indicate that this was true in 9 cases.

Restitution or spontaneous retorsion rarely occur. No instance of this phenomenon was observed, however.

There is no relation between size of a tumor and tendency to torsion. Although torsion of tumors the size of a grapefruit is frequent (52 per cent) enough to suggest an influence, the equal incidence in tumors of extreme size, namely, the size of a football or of an apple (24 per cent each), would contradict this assumption. In addition, the size has no relation to the number of pedicle turns.

POSITION OF TUMORS

Although ovarian tumor is equally frequent on both sides (44 per cent on the right side and 34 per cent on the left in 1,101 cases), torsion is twice as frequent on the right side as on the left. There was torsion of 67 tumors on the right side and of 32 tumors on the left side (69 and 31 per cent, respectively).

The relative frequency of the different ovarian tumors in given locations is as follows:

Fibroma occurs four times more often on the right side, but torsion is only twice as frequent on that side.

Torsion of papillary serous cystadenoma is three and one-half times more frequent on the right side than on the left, although the incidence of the growth is equal for the two sides.

Torsion of the simple cyst is two and a half times more frequent on the right side than on the left, although the cyst occurs only one and one half times more frequently on that side.

Torsion of a pseudomucinous cystadenoma is three times more frequent on the right side than on the left, though the incidence of the tumor is only one and one-quarter times greater on the right.

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[3] Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2, p. 1565.

A twisted dermoid cyst is found one and one-half times more frequently on the right side than on the left, although this growth occurs equally often on each side. Eleven per cent of dermoid cysts are bilateral, but no instance of bilateral torsion was found.

Fifty-seven per cent of papillary serous cancers occur bilaterally; the remainder are equally distributed on the two sides. With this type of tumor, torsion is twice as frequent on the right side.

In the group of cases reported here *not a single instance* was found of rotation with tubo-ovarian cyst or endometriosis of the ovary—conditions conducive to marked adhesions.

Thus, regardless of the incidence of these individual tumors on the right side, torsion occurs more frequently on that side.

SYMPTOMS AND PATHOLOGIC CHANGES

The clinical appearance of torsion depends on the suddenness and extent of vascular obstruction.[2] The degree of pathologic change is not proportional to the number of pedicle twists. Constitutional symptoms vary with the pathologic alterations.

Torsion may be asymptomatic if the process is slow and gradual, if rotation is less than 180 degrees or if the pedicle is long and thin; also, when there is no impairment in the flow of blood or when the rotated tumor is secondarily fixed by adhesions or loose impaction in the pelvis. A small number of women in the cases reported here were completely asymptomatic, and no change except slight edema of both the pedicle and the tumor was observed. Clear pelvic fluid and delicate adhesions may be found at this stage. Fifty-eight per cent of the tumors showed no structural secondary changes, even though as many as six or seven pedicle twists were found.

Torsion produces symptoms if vascular compression of the ovarian vessels is moderate and augmentative over a long period. Venous return becomes partially obstructed. The uterus and adnexal structures, proximal to the point of rotation, become engorged, owing to the effect on the free anastomosis medially, while the distal structures show marked edema and enlargement. Further diminution of venous return may produce hemorrhage into a cyst or its wall. Trauma, necrosis or atrophy of the pedicle have caused detachment of the tumor. Collateral circulation through adhesions to the omentum, intestine, peritoneum or neighboring structures may maintain the existence and integrity of the tumor, and it may appear to be part of another organ. Micro-organisms permeating through adherent bowel may set up an abscess followed by peritonitis and sepsis.

Twenty per cent of the patients had torsion of the types described. They complained of mild colicky pain and nausea, with occasional vomiting. Although attacks were recurrent over a three to six year period, none of the women were confined to bed and all were able to attend to their daily tasks. Constitutional symptoms were not reported.

Torsion may be sudden with severe symptoms. Acute onset was common in 80 per cent of the patients; 20 per cent of these, although many were previously not aware of the tumor, were in partial or complete shock. The remaining 60 per cent suffered acute symptoms. Agonizing colicky pain that is hard to relieve, nausea, vomiting, distention and diarrhea are the usual complaints. With abdominal hemorrhage, pains in the shoulders and chest are to be expected. The patient may suddenly, after the initial pains, become extremely distressed, apprehensive and prostrated. The abdomen becomes rigid, distended and sensitive. Rebound tenderness and signs of peritoneal irritations become manifest, while a rapid, thready pulse, fever, leukocytosis and a rapid sedimentation rate complete the clinical picture. Vaginal examination may or may not reveal a mass, since the abdominal rigidity may entirely mask the presence of the tumor.

The diagnoses of ileus, peritonitis and acute suppurative appendicitis or cholecystitis, renal colic or hemorrhage, intestinal obstruction and ruptured ectopic pregnancy were made in cases of this series. The sedimentation rate was rapid in 30 per cent (intracystic or peritoneal hemorrhage, rupture of a cyst, infarction or gangrene). In 11 per cent there was urinary urgency, and in 8 per cent, diarrhea and vomiting.

COMPLICATIONS

Complete vascular compression with thrombosis of the ovarian vessels produces marked symptoms. Pathologic complications were present in 48 per cent of the cases in this series. Infarction of the edematous wall of the cyst and solid portions of the tumor (10 per cent), as well as hemorrhage into the cavity of the cyst (30 per cent), are common. With extreme rotation, the infundibulopelvic fold (8 per cent) and the round ligament (1 per cent) as well as the fallopian tube (8 per cent) and the parametrium (8 per cent) become involved. The pelvis is occupied by a tense dark plum-colored mass, which is glistening or dull. Rupture at this time (6 per cent) may occur spontaneously in any of the twisted tissues, particularly in the pedicle, the cyst or an involved blood vessel. Free bloody fluid is fairly common (16 per cent). Bleeding into the pelvic cavity (6 per cent) with gravitation to the diaphragm (5 per cent) and consequent irritation of the phrenic nerve nearly always occurs, producing characteristic pain in the shoulder and chest. Rupture into the parametrium (3 per cent) may be followed by complete unilateral extraperitoneal extravasation of blood. The outlook for fatal hemorrhage is particularly alarming with torsion of a malignant ovarian tumor. In 1 instance of rupture of a cyst 2,500 cc. of hemolyzed blood was removed; in another instance of marked infarction with a ruptured pedicle, 1,000 cc. of blood was found. Both of the patients were admitted to the hospital in shock. Suppuration, abscess formation, necrosis (8 per cent) and peritonitis (2 per cent) may result when intestinal micro-organisms enter the tissues.

Uterine torsion is rare and bilateral twisting is very uncommon. During sexual maturity (A. Strauss), profuse and irregular uterine bleeding may be induced by ovarian torsion. Endometrial hyperplasia has been reported in this condition in the menopause. During pregnancy this accident is extremely hazardous, owing to suppuration and fatal peritonitis. Von Franque[4] stated that 20 per cent of pregnancies, accompanied by twisted cysts are interrupted. Torsion, however, practically never complicates labor.[5]

Thus, the most frequent complications of torsion are hemorrhage within the tumor, torsion of the fallopian tube and infarction. Hemorrhage into the pelvis in most cases is the most serious complication in the early stage. Torsion of the infundibulopelvic or of the round ligament is not infrequent. Rupture of the tumor or pedicle is an important factor in cases of shock. Torsion of the broad ligament and rupture into the broad ligament occur infrequently; the latter condition presents a problem in gynecological diagnosis. Varicosities of the broad ligament was an incidental finding in 1 case. In the cases of advanced torsion, infection, necrobiosis, necrosis and peritonitis may set in. A small number of patients showed these pathologic changes. Subdiaphragmatic blood is usually found in all cases of hemorrhage.

Torsion of the normal ovary, although rare, occurs principally in children.[6] An uncommon complication occurs when a twisted ovarian tumor becomes incarcerated in an inguinal hernia sac, simulating strangulation. There were no such cases in the present series.

The subsidence of pain within two or three days may mean severance of the pedicle or gangrene of the tumor, with circumscribed adhesive or spreading peritonitis. Pain in the shoulders or chest occurs within twenty-four hours after rupture (5 per cent).

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[4] Von Franque, cited by Graves.[2]

[5] Green-Armytage, V. B.: Cases of Torsion of Fallopian Tube and Ovary During Pregnancy, J. Obst. & Gynæc. Brit. Emp. **36**:87, 1929.

[6] Baron, C.: Torsion of Normal Ovary: Case of Reoccurrence of Rare Pathologic Condition, J. A. M. A. **102**:1675 (May 19) 1934. Finley, R. K.: Diagnostic Value of Uterosalpingography in Pre-Adolescent Ovarian Torsion, Surg., Gynec. & Obst. **52**:723 (March) 1931; Torsion of Normal Ovary and Tube with Rupture of the Ovary and a Review of the Literature to Date: An Addendum, Kentucky M. J. **30**:233 (April) 1932.

The complications of torsion found in various types of ovarian tumors are mentioned briefly as follows:

In 7 instances of torsion of fibroma 14 different complicating lesions were found. Hemorrhage within the tumor occurred 4 times (57 per cent) and free pelvic blood 3 times (43 per cent), and necrosis of the tumor was found (14 per cent). There were 2 instances each of torsion of the fallopian tubes and the infundibulopelvic fold (30 per cent) and 1 instance of torsion of the round ligament.

In 33 cases of torsion of a dermoid cyst there were 16 complicating lesions. The principal one, namely, rupture of the tumor, occurred 8 times (24 per cent). Infarction of a twisted fallopian tube was observed 4 times (12 per cent), and there were 2 instances each of free pelvic blood and intracystic hemorrhage.

In 3 cases of papillary serous cystadenocarcinoma with torsion there were 6 complications. Rupture of the tumor and free pelvic blood were found in 2 instances each (66 per cent). Necrosis of the tumor and a ruptured pedicle occurred once (33 per cent).

In 8 cases of papillary pseudomucinous cystadenoma with torsion, 7 complications were noted. Free pelvic blood was found 3 times (35 per cent), and there were 2 instances each of rupture and necrosis (25 per cent each).

Of 36 cases of papillary serous cystadenoma with torsion there was hemorrhage in 4 (11 per cent). Rupture and necrosis occurred twice (55 per cent each). Thus, there are 6 complicating lesions in this group of 36 cases.

In the single case of papillary pseudomucinous cystadenocarcinoma with torsion there was dilatation of the vein of the broad ligament.

MENSES

The menses were normal in 60 per cent of the patients; in 32 per cent there was hyperfunctional bleeding, namely, menorrhagia (20 per cent) and metrorrhagia (12 per cent), and in 4 per cent there was a hypofunctional menstrual condition, namely, a menopause without bleeding (4 per cent) and prepuberty amenorrhea (1 per cent). According to Graves,[2] the menstrual cycle may be altered by pelvic hyperemia induced by this condition. Dysmenorrhea was reported in only 8 of these cases.

CONCLUSIONS

1. Rotation is the most frequent (9 per cent) and dangerous complication of ovarian tumors. The treatment is always surgical.

2. Complications occur in 48 per cent of twisted tumors and depend on the degree of vascular compression. The extent of pathologic

changes and the severity of symptoms are directly dependent on the blood supply and the suddenness with which obstruction takes place.

3. The cause of torsion is unknown; factors of greatest influence are the specific weight or solidity of the tumor (75 per cent), sudden motion of the body and a tumor of moderate size (52 per cent) (the size of a grapefruit). Adhesions prohibit torsion.

4. The single complete twist is most common (37 per cent). The greatest number of pedicle turns in this series of cases was seven.

5. Ovarian tumors (1,101 cases) occur with almost the same frequency on both the right and the left side, yet ovarian torsion on the right side is twice as frequent as on the left.

6. Torsion may be asymptomatic, mild and recurrent, or extremely acute in onset with partial or complete shock. The corresponding pathologic changes of the tissue depend on the progressive or sudden vascular obstruction, varying from edema to infarction and hemorrhage.

7. Complications are rupture with hemorrhage, infarction, torsion of the fallopian tube and bloody or clear peritoneal fluid. These are in order of their frequency. Necrobiosis, gangrene and peritonitis are the end-results.

8. Torsion of tubo-ovarian cyst or of endometriosis of the ovary is not found.

9. The menses are undisturbed in most cases (60 per cent); hyperfunctional bleeding is the most frequent alteration among menstrual abnormalities. The incidence of dysmenorrhea is insignificant.

10. The diagnosis may be extremely difficult when the patient is examined in the acute stage. There is a high incidence of diagnostic error.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomalies.—Stevens [1] reviewed a series of 27 cases of solitary pelvic kidney, consisting of 25 cases reported in the literature and 2 cases which he had observed. In 1932 Collins found 572 cases of unilateral renal agenesis and 49 other probable cases reported in the literature; he added 9 cases which he had observed personally. It therefore may be presumed that approximately only 4 or 5 per cent of single kidneys are true pelvic ones. Speaking in round figures, if one may expect a solitary kidney once in every 1,000 persons, there will be a solitary pelvic kidney in 1 of about every 22,000 persons.

The indications for the treatment of ectopic kidney, surgical or otherwise, are in general governed by the well known urologic principles employed when the organ is normally situated. However, because of the relatively poor drainage and mild hydronephrosis universally present in an ectopic kidney and because of the irregular and frequently multiple blood supply, nephrectomy is more commonly demanded (when there is present elsewhere in the body a normal kidney). The blood supply of a pelvic kidney is variable; it comes from the bifurcation of the aorta. the common iliac arteries, the external or internal iliac arteries and the median sacral and other neighboring vessels. The veins usually correspond to the arteries.

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[1] Stevens, A. R.: Pelvic Single Kidneys, Tr. Am. A. Genito-Urin. Surgeons **29**:403-413 (May) 1936.

In the series of 27 cases of solitary pelvic kidney reviewed here, satisfactory descriptions of the blood supply are few. In 3 cases, including the case reported by Stevens in which surgical treatment was employed, the vessels supplying the kidney apparently came from the region of the bifurcation of the aorta only (none entering the kidney laterally), which made possible a free manipulation of the kidney for conservative measures. In 16 of the cases in which the sex was stated, 5 of the patients were males and 11 were females. The ages varied from a fetus up to 48 years. Calculus was noted 3 times, and successful operation was performed in 2 cases. In 14 cases there was some abnormality or deficiency of the sexual apparatus, which is a common finding. Many of the observations were made at necropsy, but others were made clinically in cases in which no treatment of the urinary tract was indicated. Only 11 of the patients had undergone some operation which concerned the renal condition. In 2 cases the single kidney was removed together with a neoplasm or because one was thought to be present, with, of course, subsequent anuria and death. Exploratory laparotomy was performed in 4 cases. An appendectomy was performed in 1 case. In another, the kidney, which had not been recognized, was punctured, and tissue was removed for diagnosis; in another case the kidney was mistaken for the uterus and opened, but was promptly closed. Nephrostomy was performed once and lithotomy twice; all of these operations were successful.

The gross errors were noted chiefly in earlier publications. The prevalent general use of cystoscopic and roentgenographic investigations supplies ample data to forewarn and guide the surgeon.

Gutierrez [2] stated that all anomalies of the urinary apparatus are produced by malformations of embryonic origin. All such anomalies are pathologic and are potentially surgical. Of all the anomalies that come under clinical observation, those of the kidneys and their pelves and ureters are the most common.

The table shows the multiplicity of the different types of malformation that are encountered by the urologist. The variation in the symptoms that accompany these anomalies results in many errors of diagnosis and sometimes in unnecessary operations. Pathologic conditions are more likely to be found in kidneys and ureters that are congenitally abnormal than in those that are perfectly normal. More often than not congenital malformations of the upper part of the urinary tract produce urinary retention and infection, dilatation and loss of function of the kidney, pelvis and ureter.

Anomalies of the upper part of the urinary tract fall into two classes: those that are potentially surgical and those that present definite pathologic changes. There is an enormous amount of diversity in the diagnostic and therapeutic problems presented by such kidneys. They should, however, be regarded as clinical entities, and their treatment should be chosen individually. In diagnosis, prognosis and treatment, an indispensable part is played by urography. When all renal function has been destroyed by pathologic processes, intravenous pyelography is useless for diagnosis, but it should nevertheless always be employed when ureteral catheterization is impossible. In cases of ectopic ureter, chromocystoscopy facilitates the preoperative diagnosis.

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[2] Gutierrez, Robert: Sur les anomalies pyélo-urétérales et leurs conséquences chirurgicales, Cong. franç. d'urol., Paris, 1936, pp. 194-214.

Classification of Pyelo-Ureteral Anomalies

- Calices
  - Absent
  - Ectopic
  - Abnormal in number, size or position
- Absent
- Rudimentary
- Misplaced
  - Excessively rotated
  - Not rotated
    - Anterior
    - Posterior
- Pelvis
  - Double (bifid) or multiple
    - Unilateral
    - Bilateral
  - Hydronephrosis (congenital)
    - Pelvis intrarenal
    - Pelvis extrarenal
      - Unilateral
      - Bilateral
        - Total
        - Voluminous
        - Partial
  - Diverticulum of pelvis
- Ureter
  - Anomalies of number
    - Single (one ureter absent)
    - Double on one side
    - Triple
    - Quadruple
      - Complete
      - Incomplete
    - Quintuple
    - Sextuple
  - Anomalies of form, size and position
    - Diverticulum of ureter
      - Simple
      - Multiple
    - Ureter imperforate
      - Pyo-ureter
      - Hydro-ureter
    - Stricture of ureter
      - Pyelo-ureteral
      - Vesico-ureteral
      - Median
    - Dilatation of ureter
      - Total: megalo-ureter
      - Partial: hydro-ureter
    - Golf-hole type, with reflux
    - Ureter Ectopic
      - With ectopic orifice into bladder
        - At fundus
        - Into a diverticulum
        - Near neck of bladder
      - With extravesical orifice opening into
        - Other ureter
        - Urethra
        - Genital tract
        - Intestine
    - Crossed ureters
      - With renal fusion
      - Without fusion
      - Unilateral transverse
      - Bilateral transverse
    - Ureter twisted or occluded
    - Postcaval ureter
    - Ureter with valve formation
    - Ureterocele

Treatment may be regarded as either urologic or surgical. The former is of importance for the treatment of infection and for the purpose of assuring satisfactory drainage. Surgical treatment may be either conservative or radical, according to the type of pathologic condition that is found. The results of surgical treatment are likely to be more satisfactory if the diagnosis is made early, as soon as the first symptoms arouse a suspicion as to the patient's condition.

If the function of the kidney is still satisfactory, it is possible in some cases to do a plastic operation to correct the deformation of the excretory passages. But if for lack of drainage the kidney has become hydronephrotic and has been to a large extent destroyed, nephrectomy will be necessary, provided the kidney on the opposite side has adequate function. It is evident that an anomaly of the renal pelvis may produce a urinary stasis that not only will affect the pyelo-ureteral tree but will result in complete destruction of renal function. The commonest anomaly of the pelvis of the kidney is hydronephrosis; it may be due to aberrant vessels associated with kinking of the ureter and nephroptosis. Under such conditions, conservative treatment will consist of ligation of the vessels, followed by nephrolysis, ureterolysis and nephropexy, especially if the hydronephrosis is small and the renal function sufficient. In the presence of a large congenital hydronephrosis with complete destruction of renal function, radical operation is the only recourse, if the condition of the other kidney permits. Ureteronephrectomy is indicated in cases in which both hydronephrosis and hydro-ureter are present, due to congenital malformation of the lower part of the ureter, such as an intramural stricture of a "golf-hole" orifice with vesico-ureteral reflux on one side. On the other hand, when a small congenital hydronephrosis exists as the result of pelvic retention due to lack of tone and stricture of the ureter, it may be sufficient to carry out cystoscopic treatment, with dilation of the ureters by bougies and lavage of the renal pelvis.

In certain cases in which a plastic operation is indicated, such as reconstruction or resection of the pelvis for hydronephrosis, the carrying out of a pyelo-ureteral anastomosis or transplantation of a ureter, and in cases in which it is an advantage to free the ureter from bands of adhesions and blood vessels, it may be wise first to do a nephrostomy in order to divert the urine and assure temporary drainage. This will relieve the pelvis from hydraulic pressure as well as from infection and will assure not only the restoration of good function but a sound prognosis.

In a series of 97 cases of ectopic kidney reported by Thompson and Pace,[3] the condition was discovered at necropsy in 9 cases and by physical examination or surgical exploration in the 88 remaining cases. This is an incidence of about 1 in every 1,200 necropsies performed at the Mayo Clinic and represents an incidence of approximately 1 in every 10,000 patients observed clinically. Because of the lack of symtoms which might lead to urologic investigation, renal ectopia is often discovered only at the time of surgical exploration; in 8 cases in this series the ectopic kidney was a congenital solitary organ, which fact must be carefully weighed if any one contemplates nephrectomy in cases of renal ectopia without the advantage of preoperative urographic study. Twenty-nine, or 32.9 per cent, of the 88 patients who clinically were found to have ectopic kidney suffered from recurrent pain, which indicates that the ectopic kidney as a rule drains poorly, owing either to its position or to constriction of the ureteropelvic juncture by anomalous blood vessels or perirenal tissues.

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[3] Thompson, G. J., and Pace, J. M.: Ectopic Kidney: A Review of Ninety-Seven Cases, Surg., Gynec. & Obst. **64**:935-943 (May) 1937.

Treatment such as ureteral dilation may cause harm and generally will not benefit the patient. As a general rule, if treatment is indicated, it should be surgical. Conservative operations, such as plastic procedures on the renal pelvis or ligation of anomalous vessels, are likely to fail. Nephrectomy is therefore the treatment of choice if the function of the opposite kidney will permit. The only exception is pelviolithotomy in cases in which there is little or no hydronephrosis. Pregnancy will generally be uneventful and labor normal in spite of an ectopic pelvic kidney.

Pilcher and Braasch[4] said that three anomalies of renal development which may be confused are hypoplastic kidney, renal aplasia and congenital absence of one kidney. Such malformations of the upper part of the urinary tract represent failure of proper development during embryonic life and must be clearly distinguished from atrophy of the kidney, which may follow trauma, tuberculosis and other infections, and hydronephrosis, calcareous disease or ureteral obstruction from any cause.

A hypoplastic kidney is usually from a third to a sixth the normal size, and its mate is correspondingly hypertrophied. Except for its small size it may be normal anatomically and histologically. The ureter is always patent, and excretory function may be good in regard to the elimination of urea and dye. In renal aplasia the rudimentary structure is represented by a small mass of fibrous tissue, which histologically may be composed of embryonic glomeruli and tubules in various stages of degeneration. There is no true pelvis. Congenital absence of one kidney means complete lack of development of one of paired organs. There is complete absence of the kidney, ureter and the part of the trigon on the same side. The diagnosis of these malformations is made by cystoscopic examination and intravenous urography.

A 27 year old man complained of painful, frequent micturition and pain in both flanks. Dye tests revealed a functionless right kidney. Nephrectomy was performed, and a typical hypoplastic kidney with moderate pyelonephritis was removed. The patient's symptoms were completely relieved.

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[4] Pilcher, Frederick, Jr., and Braasch, W. F.: Hypoplastic Kidney: Report of a Case, Proc. Staff Meet., Mayo Clin. **12**:52-56 (Jan. 27) 1937.

De Quevedo [5] pointed out the great frequency of polar arteries and the important part they play in the blood supply of the kidney. He observed such arteries in 19 of 30 cadavers; in 13 they were at the upper pole, and in 6 they were at the lower pole. In this study he considered as polar arteries only those supernumerary arteries which, starting at a distance from the principal trunk of the renal artery, come from the aorta and disgorge at one of the poles, and arteries which come from the renal artery at a point prior to its ramification and are directed to one of the poles. He was not concerned with normal ramifications at the hilus which are toward the poles.

In order to discover how large a portion of the renal parenchyma is supplied by such abnormal polar arteries, de Quevedo inserted into the arteries of cadavers a paraffined glass tube to which he attached a pump and a mercury manometer. Forcing water into the kidney by this route, he found that when the pressure reached 6 cm. of mercury the water passed out through the renal vein and in part through the ureter. In the course of half an hour, under constant pressure, there appeared outlined on the renal parenchyma, which was red from stasis of blood, a pale or white zone, of irregular circular contour and varying size, which indicated approximately the superficial territory of the parenchyma corresponding to this vessel. Then, to discover how far this zone extended into the interior of the kidney, he used the method of corrosion and injected substances of different colors into the polar artery and the renal artery, so that he could easily determine with accuracy the extent of renal substance belonging to each vessel. The results showed that in some cases the abnormal polar artery supplied renal substance corresponding approximately to a fourth or even a third of the entire kidney.

In view of this fact, de Quevedo suggested that in conservative operations on the kidney, whenever it is necessary to exteriorize the organ, an attempt should be made, when possible, to avoid the destruction of such an artery for the following reasons: (*a*) A portion of the parenchyma is lost through an infarct; (*b*) secondary hemorrhage is possible after infection of the infarct; (*c*) suppuration of the infarct, if it occupies a calix, may cause a postoperative urinary fistula and infection of the wound, and (*d*) in an operation like nephrotomy the amount of functioning parenchyma will be greatly reduced if the portion lost through section of the polar artery is added to the portion lost by incision.

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[5] de Quevedo, Angel: Importance des artères polaires dans la chirurgie conservatrice du rein, Arch. d. mal. d. reins **10**:269-281 (May) 1936.

It appears from a study of the literature on the subject that surgeons have not given attention to these eventualities and have not made postoperative functional tests to compare the capacity of the kidney the polar artery of which has been tied with that of the other kidney. It seems evident that when such an artery is of large caliber the functional loss entailed must be considerable.

Tumors.—Barringer[6] stated that there are many interesting data both in the literature and in the case records at the Memorial Hospital which shed a good deal of light on the effects of irradiation of tumors of the kidneys.

Investigation showed the large Wilms tumors of children to be as radiosensitive as metastatic teratomas and to undergo the same remarkable primary regression. The regression seemed to be temporary, however. The tumors grew again after perhaps a few months. When again irradiated they did not recede as readily as at first. If irradiation therapy alone was used, the disease proved fatal.

Priestley and Broders considered results of nephrectomy alone in the treatment of Wilms' tumor and reported 2 cases in which it was used; 1 patient lived thirteen years and two months, and 1 lived three years and three months, respectively, after the operation. These 2 cases are from a series of 65 cases of Wilms' tumor, in 20 of which nephrectomy was performed. One of the authors' conclusions was as follows: "The group who were treated by irradiation and nephrectomy survived approximately twice as long as the group who were treated by operation or irradiation separately. No patient to our knowledge has been cured of Wilms' tumor by irradiation alone." Alcock, in a personal communication to Barringer, stated that among nephrectomized patients the mortality in the first eighteen or twenty-one months was just 100 per cent. Other authors reported that 90 per cent of children die in the first year after operation. The operative mortality is between 15 and 30 per cent. In a large number of cases the lesion is inoperable.

In consideration of the results of irradiation followed by operative removal, Randall has reported several cases, but in none of them did the patient survive long after nephrectomy. Alcock reported a tumor of the kidney in a girl 3½ years of age. The tumor was irradiated for six weeks, and the kidney was removed. The child was alive and well approximately three years after she was first seen. Barringer had 2 patients, 1 of whom died six months after admission and four months after an easily performed nephrectomy. The record in cases in which a tumor of the kidney has been removed after irradiation is not brilliant. The life span of the patients has apparently not been much lengthened. Unquestionably, the operative hazard is less if the kidney becomes smaller after irradiation. Barringer stated that surgeons have been too impatient to remove the tumor after irradiation. Ewing has emphasized this. As far as one can see from case records, most surgeons have so indulged themselves. Barringer expressed the belief that the time of election for removal of such a tumor is when it has reached its maximal regression after irradiation, which generally requires from one to two months. He was convinced that irradiation should be continued somewhat longer and that operative removal should be deferred as long as possible.

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[6] Barringer, B. S.: Radio-Sensitive Kidney Tumors, Tr. Am. A. Genito-Urin. Surgeons **29**:415-427 (May) 1936.

Cutting into a tumor composed of highly malignant cells would seem theoretically at least to be perilous. In 4 of Barringer's 10 cases, because of squeezing the kidney or cutting or breaking into it at the time of operation, there were rapid local recurrences. In 1 of these cases there had been inadequate preoperative irradiation of the kidney. One could not help coming to the positive conclusion that incision of such a tumor for the purpose of diagnosis should not be done. If the kidney is not removed, one should be content to rest the diagnosis on the pyelogram, the tumor and its reaction to irradiation.

Theoretically, the trauma resulting from the exploration, the attempt at removal or the actual removal of a Wilms tumor is an ideal method of releasing tumor cells, which enter the blood stream and cause distant metastasis. In 6 of Barringer's 10 cases there was distant metastasis; 4 patients had undergone nephrectomy, 1 had been subjected to nephrotomy and 1 had not had any operation. In the 4 cases in which there was no distant metastasis 4 of the patients had undergone either nephrectomy or nephrotomy. These cases are too few to give much support to this theory. Transperitoneal nephrectomy is the operation of choice and should prevent metastasis in a certain percentage of cases.

In Barringer's series, as measured by the pathologic reports on removed and irradiated kidneys and by end-results, sufficient irradiation to control the primary tumor was not or could not be given. By observing the effects of irradiation on children, one is impressed with two reactions. Apparently, the skin of children stands irradiation better than that of adults, but the general condition of children is more affected. In particular, leukopenia develops; the hemoglobin content and the number of erythrocytes remain the same or even increase. Rarely, irradiation causes severe and even fatal bleeding. There was 1 such case at the Memorial Hospital. Barringer has been able to collect from the literature and the records of the Memorial Hospital reports of 6 cases in which irradiation alone has apparently controlled the disease.

Kirshbaum and Culver[7] reported 2 cases in which sarcoma originated in the region of the renal hilus: a fibrosarcoma and a mixed tumor with sarcomatous elements. The true character of the neoplasm in each instance was not suspected before operation. The diagnosis was made from the pathologic examination of the excised specimens. Clinically, this condition presents vague symptoms, and the diagnosis is usually made very late. It may be well to remember that a tumor found compressing the kidney may have its origin in the renal hilus, which may help to explain the origin of some of the obscure sarcomas situated either in the perirenal or in the retroperitoneal tissue.

Roth and Davidson[8] reported a case of pulsating metastatic hypernephroma of the sternum. This case is unique in that an additional primary neoplasm was present in the brain. Primary pulsating neoplasm of the sternum has not been reported. Cases have been reported of pulsating neoplasm of the sternum which was secondary to hypernephroma or to malignant adenoma of the thyroid gland. In the absence of an aortic aneurysm and demonstrable neoplastic changes of the thyroid gland, a pulsating sternal mass should be strongly suspected to be a metastatic hypernephroma, even though clinical evidence of a primary renal tumor is wanting. An apparently solitary metastatic hypernephroma of the sternum is likely to be accompanied by silent, undetected metastasis elsewhere, and surgical intervention is therefore inadvisable.

Perrier[9] reported a case of carcinoma of the pelvis of a horseshoe kidney in a girl aged 4 years. The first symptom was a violent attack of hematuria, unaccompanied by any other signs of renal disturbance. Urinalysis done three times in the course of ten days showed sterile hematuria, with no further changes other than the presence of a few hyaline cylinders. Catheterization revealed that the blood came from the right kidney. Careful palpation revealed nothing abnormal, and the child played, ate and slept as usual. When chromocystoscopy and roentgenography both gave negative results, Perrier was compelled, by exclusion, to consider the idea of a tumor of the right renal pelvis, notwithstanding the rarity of such a condition in a child.

A lumbar operation, performed two months after the first sign of hemorrhage, revealed the presence of a horseshoe kidney and a soft tumorous mass in the right side of the pelvis. The two kidneys were united at the lower poles by an isthmus of true renal parenchyma. Perrier divided the isthmus and removed the entire right half of the horseshoe organ. Operation was followed by prompt recovery, and the child was dismissed in good condition twelve days later.

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[7] Kirshbaum, J. D., and Culver, Harry: Sarcoma of the Renal Hilus, Surg., Gynec. & Obst. **64**:944-948 (May) 1937.

[8] Roth, L. J., and Davidson, H. B.: Metastatic Pulsating Tumors of the Sternum Secondary to Renal Hypernephroma, J. Urol. **37**:480-489 (April) 1937.

[9] Perrier, M.: Carcinome du bassinet d'un rein en fer à cheval, J. belge d'urol. **5**:357-363 (Oct.) 1936.

The pathologic examination revealed within the pelvis of the kidney a friable neoplastic mass which microscopically had the character of a carcinoma of the renal pelvis. It had started at the free pole, at the level of a flattened papilla, where it became integrated with the point of the pyramid; here, it had the form of a pavement epithelial growth, but as it advanced farther from its starting point it gradually lost its alveolar structure and finally became a solid carcinoma, thus presenting a rather unusual type of architecture.

The prognosis of these tumors must be reserved, especially in young children, as recurrences are common even after three or four years. This case is of special interest etiologically, in view of the presence of a horseshoe kidney, which points to the existence of a congenital anomaly of the calix, in which it had its site, as the original cause of the neoplasm.

Dean [10] discussed a few of the fundamental factors concerned with preoperative irradiation in the management of renal tumors.

Realizing the diagnostic importance of a histologic examination and hoping that by its aid an early differentiation between radiosensitive and radioresistant tumors could be obtained, Dean has obtained biopsy specimens by aspiration from all suspected renal tumors for the last eighteen months. The technic is not difficult, and no patients have been harmed as far as he knows. After examining the smears a skilled pathologist can make a positive or negative diagnosis of tumor, but grading has been impossible and predictions regarding radiosensitivity cannot be made.

Preoperative irradiation of renal tumors has been recommended to devitalize tumor cells and thereby lessen the likelihood of disseminating metastasis by operative manipulations. Little proof exists that metastasis is promoted by careful operation. Furthermore, if it were a common occurrence it is doubtful whether preoperative irradiation could completely eliminate the danger. Even in those tumors in which the most marked regression has been obtained by irradiation, one can usually find a certain amount of apparently viable tumor tissue. However, until there is more exact knowledge on this point it is more conservative to reduce the possibility of metastasis in any practical way.

Preoperative irradiation of renal tumors has also been recommended to diminish the size of the tumor and make nephrectomy easier. This is an important effect of irradiation and is of much clinical importance. A large proportion of the tumors of the renal parenchyma in adults and the great majority of Wilms tumors in children shrink when irradiated. Only a therapeutic test will determine how much an individual tumor will respond, but the benefit may be so marked that the preoperative irradiation of all large renal tumors is recommended.

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[10] Dean, A. L., in discussion on Munger, Arbor D.: Irradiation of Malignant Renal Neoplasms, J. Urol. **37**:692-694 (May) 1937.

Preoperative irradiation of renal tumors has also been recommended to make inoperable tumors operable. In this discussion an uncomplicated primary tumor was not classified as inoperable because of its large size alone.

It is important to know the amount of radiation which can be delivered to the average renal tumor. With a voltage of 200 kilovolts to the anterior, posterior and lateral portals, each as large as the size of the patient's body permits, at a target-skin distance of 70 cm., and in divided doses of 300 roentgens to one portal daily, filtered through 0.5 mm. of copper, it is possible to give most patients 2,400 roentgens to each portal in about twenty-six days. In treating infants, 200 roentgens per day at a distance of 50 cm. has been effective. No attempt should be made to give a predetermined total dose to these small patients. Careful examinations should be made before each treatment. The effects of irradiation can best be gaged by the clinical changes noted from day to day.

The value of a preoperative cycle of irradiation which may deliver a maximal dose of 5 threshold erythema doses to a tumor depends largely on the cellular make-up of the growth. Epithelial tumors of the renal pelvis are radioresistant. For this reason and because they tend to remain localized for a long time and because obstruction and infection usually are present, preoperative irradiation is not recommended. At the opposite extreme of radiosensitivity are Wilms tumors, which usually are composed of embryonal tissues. Because these tumors are large when discovered and because they usually regress readily under irradiation, preoperative treatment is of the greatest value. Tumors of the renal parenchyma in adults generally are of an intermediate radiosensitivity, but there may be considerable differences within the group. Preoperative irradiation is recommended in these cases. With the present inadequate knowledge and until more powerful sources of irradiation are provided, it is probably safer to regard preoperative irradiation strictly as an adjunct to operation.

If a growth is radiosensitive, regression will be prompt and rapid. Perhaps the tumor will disappear after only a part of the maximal dose of irradiation has been given. Since this is as much regression as can reasonably be expected, nephrectomy can be performed without further delay. For a tumor which is more radioresistant it may be necessary to give a full dose of radiation and wait a few weeks before the greatest possible regression takes place. However, little is to be gained by a delay of more than a month.

Dean has found that healing of nephrectomy wounds may be delayed by heavy irradiation, but so far this disadvantage has been of relatively little practical importance.

Jasienski,[11] on the basis of a case which he observed, pointed out the ease with which one may mistakenly diagnose, by means of pyelography, a hydronephrosis that does not exist. In this case it was believed that the patient was suffering from a hypernephroma of the right kidney, complicated by hydronephrosis. The patient died in a few days, and necropsy revealed that the right kidney was not enlarged but that it actually was smaller than the left one, which was healthy. Its position, however, was abnormal, which had led to misinterpretation of the pyelogram. On its upper surface was an enormous hypernephroma, and around it there were several other solid tumors, above, below and outside of the organ. These growths had crowded the kidney out of its proper position and had pushed it toward the median line and the anterior ventral wall. The majority of surgeons are satisfied to make a single pyelogram with the patient in the dorsal position, which ordinarily gives a correct view of the positions of the calices, pelvis and ureter. But this case shows that under certain conditions the image of the pelvis filled with opaque fluid as it is seen in the roentgenogram may not be in accordance with the true state of affairs and may lead to an erroneous diagnosis. It teaches that pyeloscopy is the only method that can prevent such errors, since it permits the exploration of the image of the renal pelvis under the roentgenoscope and in all directions, and that hydronephrosis can never be confused with a shadow due to an abnormal position of a kidney. In the pyelogram, however, since the tumor had displaced the kidney, the shadow of the renal pelvis was much larger and much farther from the median line than the organ was in reality. Only pyeloscopy, or else a second pyelogram taken with the patient in the ventral position, would have been adequate to prevent the erroneous diagnosis that was reached. In this case, owing to the fact that the pelvis was dilated and that it constituted in any event a sound reason for operating, the failure to make an exact diagnosis had no adverse effect on the patient's welfare, but the experience shows the greater exactitude of pyeloscopy as compared to pyelography.

Stone.—Randall[12] offered a preliminary report to prove that a renal stone originates by growth on an initiating lesion. Secondarily, the fact that such an initiating lesion must be sought for on the renal papilla has, in his opinion, likewise been proved in the microscopic work performed and by the findings related, for he has been fortunate in the material available, as he found rather typical progressive steps in the growth of a calculus. He also described a pathologic process occurring in the wall of the renal papilla which hitherto has not been recognized and which consists of a subsurface deposit of calcium.

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[11] Jasienski, G.: De la radiographie des voies urinaires dans les tumeurs solides du rein, J. d'urol. **42**:543-548 (Dec.) 1936.

[12] Randall, Alexander: The Initiating Lesion of Renal Calculus, Tr. Am. A. Genito-Urin. Surgeons **29**:323-330 (May) 1936.

In the series of cases presented Randall stated that he had traced from the subsurface deposit of calcium the destruction of its covering surface membrane and the deposit thereon of two characteristic types of urinary salts—calcium phosphate and calcium oxalate. These salts appear to be direct secondary deposits on this calcium plaque once it is denuded of its epithelial covering. It was his belief that once such a calcium plaque has lost its covering membrane and is bathed in the urinary excretion, there then are deposited on this plaque, as a foreign body, certain salts normally present in the urine, and the salt so deposited follows closely the well recognized laws of the crystallization of salts from any solution wherein seeding for crystallization and supersaturation play the dominant rôles and are the determining factors as to the character of salt to be deposited. He did not presume that the described pathologic stages constitute the sole initiating lesion on which all stones originate but reserved for further study the possible relationship of focal infection, septic and aseptic ulceration, infarction, allergic reactions of mucous membrane and keratinization from avitaminosis.

Gabrielle and Girgensohn[13] stated that urinary stasis, whether septic or aseptic, is undoubtedly one of the most important factors in the pathogenesis of renal lesions. While there is a large literature concerned with the results of aseptic stasis, there is little knowledge of the mode of propagation of inflammatory processes of pyelic origin, since the relation between urinary stasis and ascending infection has not yet been ascertained.

The authors undertook experiments with the injection of india ink into rabbits, with a twofold purpose: (1) to ascertain the mode of diffusion of the nonbacterial contents of the renal pelvis during the course of an exaggerated pressure exerted on them by stasis of various types and duration and (2) to determine the routes of ascending infection and, for each route, the specific changes occurring in the renal parenchyma. In the second series of experiments an infection of the renal pelvis was provoked in the course of these various types of urinary stasis.

It was found that an acute increase of pressure within the renal pelvis causes rupture of the fornix, associated with injection of the lymphatic and venous systems. But rupture does not occur when as a result of a long-standing chronic urinary stasis the fornix is able to assume a rounded form and hydronephrotic atrophy becomes manifest. These anatomic modifications can be found at the end of the first week after ligation of the ureter or at the end of the second week after artificial production of a ureteral stenosis.

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[13] Gabrielle, S., and Girgensohn, H.: L'influsso della stasi urinaria sulla diffusione nel parenchima renale del contenuto pielico asettico e settico, Arch. ital. di urol. **13**:519-547 (Sept.) 1936.

With the appearance of this hydronephrotic atrophy, pyelovenous reflux and injection of the lymphatic system cease simultaneously. There is not enough rounding of the fornix in acute dilatation to prevent its rupture. It is only in chronic urinary stasis due to hydronephrotic atrophy that stabilization of the modification of the form of the fornix is achieved and renders it capable of successfully withstanding the increased pressure within the renal pelvis. It was possible in such a pelvis to reach a degree of pressure that would overcome the mechanism of closing of the papilla and cause an injection of the tubules, which increased as the dilatation of the pelvis went on. It was of interest that in a certain group of kidneys in which there were cicatrices of the cortex of unknown origin the spontaneous changes observed were sufficient to cause evident injection of the tubular system accompanied by prompt rupture of the fornix; partial modifications of the symmetry of the fornix also led in the same direction.

In the second series of experiments it was observed that ascending infection is diffused as follows: In the normal kidney infection rarely finds an entry. But when there is pyelitis, the infection is diffused almost exclusively to the lymphatic system through the fornix. This lymphogenous propagation is present in all degrees of urinary stasis, up to the point where the fornix disappears through the effect of the progressive hydronephrosis.

In hydronephrosis the phenomena of lymphangitis are totally masked by the rapid propagation of the bacteria into the urinary canaliculi. Within a few hours the lymphangitis has reached the renal cortex, where it immediately causes inflammation. But it is only the association of bacteria which arise in the renal pelvis with those that are eliminated from the cortex by means of the urinary flow that governs the occurrence of grave inflammation and necrosis of the medullary cone. These changes dominate the disease picture of the last stages. The more the hydronephrotic atrophy progresses, the more impervious do the canaliculi and the lymphatic vessels become; they cause the infection to slow up and to progress with more and more difficulty.

If in a normal kidney an infection of the pelvis is produced simultaneously with an acute urinary stasis by the tying of the ureter, rupture of the fornix occurs on the second or third day afterward. Diffusion of the contents of the renal pelvis then causes an abscess of the hilus of the kidney, which is accompanied at the same time by a rapid spread of the infection through the tubules and, more slowly, by a spread through the lymphatics. Only in the initial stages, however, can the individual modes of propagation be recognized, some one of which is generally found to predominate over the others. In the later stages it is not possible to establish any distinction between the several routes by which the infection has been disseminated.

McCague[14] reported a study of the problem of traumatic renal and vesical calculi.

Stones form in stone-free patients who are immobilized for long periods because of fractures of the long bones, lumbar vertebrae and bony pelvis and also because of osteomyelitis. This is an important clinical problem, as grave injury may take place; in some instances it may result in urosepsis and death. In all cases the following factors are constant: urinary stasis, urinary infection, alkaline urine and the stones, which are phosphatic. A plan for the prevention of the formation of this type of stones was suggested.

The major problem is that of prevention. In all cases of fracture patients who are potentially liable to have stones are carefully studied as to their status on admission. The character, bacteriology and p_H of the urine are noted, Jean's test is performed, the urinary tract and the bony skeleton are examined roentgenographically and quantitative tests are made for serum calcium, phosphorus, protein and phosphatase. In this group of cases rigid measures to prevent the underlying causes of the formation of stones are put in operation at once.

If the patient is immobilized in a fracture bed,. frequent elevation of the renal level is made to combat stasis by changing the position consistently with the treatment of the particular fracture. Extreme care is used in any instrumentation that may be necessary. Elimination of any foci of infection is effected when possible. The patient is immediately placed on an acid ash diet with an excess of acid ash of from 20 to 30 cc., dependent on the hydrogen ion concentration of the urine. An attempt is made to keep the p_H of the urine between 5 and 5.2. Enteric-coated pills containing about 7½ grains (0.49 Gm.) of ammonium chloride are given three times daily. Fluids are forced; a minimum of 3 liters per day is given. At the same time that the plan for prevention is in operation, the patient is carefully studied to determine a possible cause of the formation of stones.

Oppenheimer and Pollack[15] followed the method of Higgins in an attempt to secure solution of renal calculi by dietetic measures. Twenty-seven patients were placed on the diet for from six to sixteen months; the average period was eleven months. Twenty of the patients maintained a mean urinary p_H of 5.2 or less. In no case was a complete or partial solution of the urinary calculus noted in the roentgenograms, which were made frequently. Five patients showed an increase in size of their renal calculi, and in 1 case a new stone formed while the patient was on the regimen. In the authors' experience the high vitamin, acid ash diet did not cause a disappearance or reduction in the size of renal calculi of the alkaline earth type.

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[14] McCague, E. J.: A Preliminary Report on a Study of the Problem of Renal and Vesical Calculi that Occur in the Traumatic Group, Tr. Am. A. Genito-Urin. Surgeons **29**:331-336 (May) 1936.

[15] Oppenheimer, G. D., and Pollack, Herbert: Attempted Solution of Renal Calculi by Dietetic Measures, J. A. M. A. **108**:349-352 (Jan. 30) 1937.

Twinem [16] reviewed 314 cases in which operation was performed for nephrolithiasis. The percentage of recurrence after pyelotomy was 20.9, and that after nephrotomy was 28. The greater incidence after nephrotomy agrees with the results of other investigators, but this point should be interpreted with some qualification since the type of operation originally selected depends on the size, shape, number and situation of the stones. The percentage of recurrence after operations for multiple calculi was greater than that after operations for single stones. The frequency of pseudorecurrence is considerable, and to avoid this possibility, roentgenograms should be taken at the time of operation, particularly in cases of multiple and stag-horn calculi.

The low percentage of recurrence in the opposite kidney after both nephrectomy and conservative operation indicates the significance of local factors in the formation of stones. Phosphatic calculi were found to recur more frequently than calculi of other composition except those composed of cystine. In the 10 cases in which stones recurred the kidneys most frequently were either primarily or secondarily infected. The importance of Bacillus proteus in these cases was emphasized. Methods of avoiding postoperative recurrence were outlined. In 56 cases in which the patients have been treated along these lines for the past year and a half, there has been a recurrence in 5.36 per cent. The possibility of the presence of hyperparathyroidism should be investigated, particularly in cases of bilateral and recurring lithiasis.

Frankenthal [17] reported 2 cases in which cystinuria occurred in sisters; in 1 case there were two stones in the renal pelvis; in the other case there was a hereditary atrophy of the macula in the fundus of each eye. Frankenthal debated whether cystinuria should not be considered a definite mark of degeneration, as it often is found in different members of the same family. It is generally admitted today that cystinuria is a pathologic change in the metabolism of amino-acids. Important for diagnosis is a careful daily examination of the urinary sediment in order not to miss the characteristic cystine crystals. Therapy must be as conservative as possible, because the stones recur easily. Diet should be poor in proteins, and large doses of sodium bicarbonate should be administered.

Domanski [18] presented a scheme for the analysis of the components of renal calculi. The system of analysis described did not include a test for every presumably possible component of renal calculi. Specificity and simplicity of procedure were the chief concern. The selected list of substances to be identified were those commonly encountered in the chemical laboratories of the Jersey City Medical Center, and it has been found adequate in dealing with 35 consecutive mixed renal calculi.

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[16] Twinem, F. P.: A Study of Recurrence Following Operations for Nephrolithiasis, J. Urol. **37**:259-267 (Feb.) 1937.

[17] Frankenthal, L.: Ueber Cystinurie und Cystinsteine, Arch. f. klin. Chir. **187**:414-424 (Jan.) 1937.

[18] Domanski, T. J.: Renal Calculi: A New Method for Qualitative Analysis, J. Urol. **37**:399-406 (March) 1937.

The stone is placed on a clean piece of filter paper, moistened with alcohol and scraped free from adherent blood with a scalpel. The specimen is then sawed in half along its shorter axis and examined for the presence of nucleus and stratification. When the latter is present, there may occur a great many layers. Actually, there has never been found a subsequent clearcut chemical difference between more than two alternating varieties. Preparatory to chemical analysis, the stone, or a portion thereof, is ground to a fine powder in a small glass mortar with a glass pestle. Separate layers and nucleus are treated in the same way. The following scheme of analysis is then followed:

To test for uric acid and urates, one should sprinkle a small quantity of the original pulverized sample into a small porcelain casserole. A few drops of concentrated nitric acid should be added and the mixture evaporated to dryness on a water bath. A red color signifies uric acid or urates or both.

Weidel's test, when negative for uric acid, produces a lemon-yellow residue. To test for xanthine, one should add a few drops of a concentrated solution of sodium hydroxide to this residue. In the presence of xanthine a red color is produced.

To test for cystine, one should add from 5 to 10 cc. of ammonium hydroxide (20 per cent) to a small portion of the original pulverized sample, shake vigorously for a few minutes, filter and place a few drops of the filtrate on a clean slide. On the evaporation of ammonia, the characteristic flat hexagonal crystals of cystine can be recognized microscopically under the low power objective.

The presence of phosphates may be determined by placing a small amount of original pulverized sample in a pyrex tube and adding about 5 cc. of ammonium molybdate reagent and an equal volume of concentrated nitric acid. After it is carefully heated to the boiling point, a yellow precipitate appears if there are phosphates.

To test for carbonate, one should add approximately 10 cc. of 10 per cent hydrochloric acid to a portion of pulverized sample. The evolution of gas (carbon dioxide) indicates carbonate (as calcium carbonate).

To test for oxalate, the hydrochloric acid mixture prepared for the carbonate test should be filtered and the filtrate placed in a small casserole. It should be made alkaline to litmus with ammonium hydroxide (15 per cent) and then just acid with acetic acid (5 per cent). After it stands for at least half an hour, it should be centrifugated at high speed until the precipitate, if any, is firmly packed at the bottom of the tube. Most of the supernatant solution should be decanted, and a drop of the sediment should be placed on a clean slide and examined microscopically under a low power objective for the characteristic crystals of calcium oxalate. The appearance of a crystalline precipitate in the acetic acid solution is indicative of oxalate.

All the stones analyzed by Domanski at the time of his report had been "mixed" stones. In each case more than one substance had been isolated and identified. He did not consider these facts unusual in the light of the medium in which the stones are formed, the possibilities of coprecipitation and the high insolubility of the salts separately considered. The occurrence of phosphates appears universal. Even in the case of a "pure" uric acid stone, appreciable quantities were found. Calcium oxalate almost always accompanies phosphate but usually in relatively smaller quantities; calcium carbonate less frequently accompanies phosphates and most often in quantities small enough to merit the term "impurity."

Tuberculosis.—De Illyès [19] pointed out that urogenital tuberculosis is always secondary to some primary focus elsewhere in the body, which may exist in the form of a cured process and may or may not be detectable. The primary focus most frequently is situated in the lung or in some of the lymph nodes in the hilus or the mesentery. Within the urinary organs themselves, the primary focus is most often the kidney; within the genital organs, it is most often the prostate gland. Both of these are important centers, and there are innumerable modes of propagation. The simultaneous condition of the urinary and genital organs is very common; but of these organs, the kidney is most frequently infected.

At the clinic of the University of Budapest, in 1,071 patients, or 52.4 per cent of 2,043 operated on for purulent infection of the kidney, the condition was tuberculosis. After long study and experimentation, de Illyès concluded that the presence of tubercle bacilli in the urine does not justify the conclusion that there are tuberculous changes in the kidney unless at the same time pus is found in the sediment of the urine. This is a sign of inflammatory reaction caused by the bacillus. To diagnose tuberculosis, the presence in the urine of pus provoked by the Koch bacillus is absolutely necessary. It is known that in the normal kidney the filament of the glomerulus does not allow the tubercle bacillus to pass, but that pathologic changes which arise in the kidney may allow it to penetrate into the urinary tract, or that because of the slowness with which the blood circulates in the filter the tubercle bacillus arriving there may remain so long in contact with the wall as to produce a toxin and lead to tuberculous nephritis and albumin or cylinders in the urine.

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[19] de Illyès, Géza: La tuberculose urogénitale, J. d'urol. **42**:309-326 (Oct 1936.

which are due to degeneration of the renal parenchyma. In the laboratory of de Illyès some of the experiments showed that after the injection of large quantities of tubercle bacilli into the circulation none of these has ever been found in the renal canaliculi in less than one week afterward, that is, not until there had been time for a specific change to occur, as was found by dissection. On the other hand, there were instances in which millions of bacilli had been injected into the circulation for thirty-six days, yet one was never found in the urinary canals after dissection.

In cases of early tuberculosis of the kidney, the exact localization can be found by separate catheterization of the two kidneys, while there is still no change at the vesical orifice of the ureter. In cases in which medical examination does not furnish indubitable proofs of tuberculosis, it is advisable to wait some weeks or even months; this does no harm and will make possible the finding at a later time of proper indications for operation. In every case the moment for establishing such indications should be weighed with great care, since when one removes a kidney one removes the organ which is the most important for the production of antitoxin. One should accordingly not operate too early, even if 4 of 6 patients are going to die from the disease at a later time. Both in early infection and also in advanced infection that has been neglected, and in cases in which tuberculous ulcers have rendered cystoscopy impracticable, diagnosis is difficult; however, in typical infections, such as are seen daily, the Ziehl-Neelsen stain makes diagnosis easy, and pyelography is rarely necessary.

De Illyès has never seen a patient who had renal tuberculosis recover spontaneously, but he has seen a tuberculous kidney become cavernous and caseous, the ureter become thick walled and an autonephrectomy result, so that the patient feels practically well again.

In cases in which the infection is bilateral the author is loath to operate and first tries every possible kind of treatment, including the Gerson diet, injections of the type described by Sailer (iodine-guaiacol-pancreas-lipase), injection of the tubercle bacillus vaccine described by Vaudremère and sometimes roentgen irradiation, which occasionally is favorable.

Of 617 patients who underwent nephrectomy for renal tuberculosis during the fifteen years from 1920 to 1935, 119 were alive and in good condition and 322 were in poor condition. The former were chiefly intellectual persons who were able to live under conditions of material comfort, and the latter were mostly persons who belonged to the laboring class. Twenty-five per cent of the latter were able to resume their work.

The article contains an excellent bibliography.

Mathé[20] reported 6 cases of unilateral renal tuberculosis in children and adolescents. Four of the patients were living and well eight years, six years, eleven months and three months, respectively, after operation. One died six months and 1 died five years after operation, because of generalized dissemination of the disease.

In reviewing 4,698 cases of unilateral renal tuberculosis, Mathé found that 565 (12 per cent) of the patients were from 1 to 20 years of age, 0.42 per cent were from 1 to 5 years, 1.08 per cent were from 5 to 10 years and 10.5 per cent were from 10 to 20 years. Necropsy statistics have demonstrated the incidence to be much higher (from 25 to 30 per cent).

In spite of the invention of a perfected small caliber cystoscope for use with children, the more general use of tests for renal function and the use of the roentgen rays, many pediatricians and physicians still fail to take advantage of these improved and more accurate methods of investigation in cases in which children are suffering from chronic infection of the urinary tract.

Mathé emphasized the importance of bearing renal tuberculosis in mind when making a urologic examination of children who have chronic cystitis, persistent pyuria and relapsing pyelitis.

Although clinical quiescence and autonephrectomy have been overenthusiastically hailed as spontaneous healing of renal tuberculosis, nephrectomy is the treatment of choice for the unilateral type, which affects children as well as adults, and if this operation is performed sufficiently early it is followed by a large percentage of cures.

Lett[21] stated that renal tuberculosis is not a primary and independent disease; it is a local manifestation in a tuberculous subject and is a result of a systemic infection.

In London and the surrounding districts, renal tuberculosis is comparatively rare. An analysis of the records of the London Hospital showed that among 116,713 patients admitted to the surgical wards during the twelve years from 1923 to 1934 there were only 208 who had renal tuberculosis, and in more than a third of these nephrectomy was considered inadvisable on account of their serious condition and the presence of active tuberculosis elsewhere or because the disease was bilateral. In Paris, on the other hand, no less than 568 nephrectomies were performed in Marion's clinic during the ten years from 1919 to 1928. Lett stated that 20 per cent of the patients admitted to urologic clinics suffer from renal tuberculosis and that of a series of 100 consecutive operations on the kidney 50 were performed on patients who were suffering from this disease.

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[20] Mathé, C. P.: Juvenile Tuberculosis of the Kidney: Diagnosis and Treatment, Surg., Gynec. & Obst. **63**:283-292 (Sept.) 1936.

[21] Lett, Hugh: Renal Tuberculosis: Early Diagnosis and Treatment, Lancet **2**:1313-1318 (Dec. 5) 1936.

The onset of renal tuberculosis is insidious and may be symptomless. Repeated examinations of the urine should be made, especially in every case in which a patient is undergoing treatment for extra-urinary tuberculosis.

In some cases early renal tuberculosis can be cured by medical treatment provided that the condition is recognized before there is any alteration in the renal calices.

Unilateral renal tuberculosis becomes a surgical problem as soon as pyelograms show the changes characteristic of the disease, for it is then beyond the hope of cure by medical means alone.

The patient may be free from disturbing symptoms for prolonged periods, but the disease will almost invariably progress and ultimately prove fatal unless the kidney is removed.

Treatment in a sanatorium should always follow nephrectomy and in some cases precede it, as renal tuberculosis is not a primary disease; it is always secondary to a systemic infection and indicates a lowered resistance to the tubercle bacillus. The close cooperation of the general practitioner, the physician and the surgeon is desirable and indeed essential.

Remete[22] reported a series of 30 cases of tuberculosis of the urogenital tract or tuberculous fistulas of long standing after operation. Blood cultures were made for tubercle bacilli by the method of Löwenstein.

He came to the following conclusions: In active tuberculosis of the urogenital tract, tubercle bacilli could never be found in the blood. The same was true in cases in which fistulas followed removal of a tuberculous organ. Tuberculous bacteremia is rare, and its finding does not aid in the early diagnosis of urogenital tuberculosis.

Hydronephrosis.—Solcard and Pervés[23] reported a case of hydronephrotic horseshoe kidney. The patient was a man aged 21 years, who apparently was in good health except for intermittent bilateral pains in the lumbar region and the presence of a soft tumor, which was the size of a mandarin orange (tangarine), situated to the right of the umbilicus and adherent to the deep tissues. Movements of the tumor were restricted vertically, but it could be moved transversely and from within outward; such movement caused pain on both sides in the lumbar region.

The first diagnosis was hydronephrosis of abnormal form on the right side, but catheterization revealed a hydronephrotic horseshoe kidney which extended in a frontal direction and tended to resemble the "L-shaped kidney" of Papin. Roentgen examination showed that on the right side the catheter followed a normal course, whereas on the left it deviated to the right on reaching the promontory of the sacrum, crossed the vertebral column and stopped a short distance beyond this point. The injection of air revealed a normal pelvis and calices on the right side; on the left, however, there was an enormous pocket which was outlined transversely in front of the vertebral column; 150 cc. of opaque fluid could be injected before the distention became painful. After pyelography, however, a high temperature developed; the urine became purulent and contained streptococci, Bacillus perfringens and a virulent strain of colon bacilli, none of which yielded to treatment with serum. Toxemia was so severe that a transperitoneal nephrectomy could not be performed; therefore, expectant treatment was carried out. It was not until forty days after pyelography that an attempt was made to find the iliac portion of the left ureter, to fix it to the abdominal wall and to dilate it and drain the infected pocket, which was found to contain 100 cc. of thick and fetid pus. Peritonitis developed, and the patient died.

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[22] Remete, Tibor: Zur Frage der Koch-Bazillenzüchtung aus dem Blute bei den tuberkulösen Erkrankungen der Harn- und Geschlechtsorgane, Ztschr. f. urol. Chir. u. Gynäk. **43**:49-57 (Feb.) 1937.

[23] Solcard and Pervés: Hydronéphrose infectée, et péritonite mortelle consécutive, dans un cas de rein en fer à cheval, Arch. d. mal. d. reins **10**:291-297 (May) 1936.

At partial necropsy injection of iodized poppy-seed oil 40 per cent into the arterial system of the kidney showed that the kidney was poorly vascularized. It is certain that a pathologic kidney which has a poor blood supply and is associated with retention and separated from the intestine only by the peritoneum must become infected sooner or later. One may say that the traumatism inflicted by the pyelography facilitated infection; in addition, as the usual bromide solution was not available, the authors injected colloidal silver, which, although theoretically aseptic, is more dangerous. It has been said to cause irritation of the renal pelvis and calices. In reviewing the case, the authors were inclined to believe that if they had performed a transperitoneal nephrectomy (this was the only procedure that seemed to offer any hope of success, owing to the peculiar form of kidney), they might perhaps have saved the patient, or that after infection had closed the peritoneal route against them they should have performed an iliac ureterostomy at once, since a pyelotomy on a median pus pocket surrounded with vessels and already bound down by adhesions was too dangerous. At any rate, they agreed with Tourtou in the opinion "that in congenital malformations one should be much more of an 'interventionist' than in kidneys normally situated."

Astraldi and Repetto[24] reported an unusual case, in which a bilateral hydronephrosis which was due to inferior polar vessels was accompanied by bilateral calculosis. The patient was a girl aged 14. Since about the age of 8 years she had had bilateral pain in the lumbar region. She had had pain in the hypogastrium and several attacks of renal colic; one of these attacks had been associated with hematuria. General malaise and intense asthenia finally had developed. The disproportion between the relatively small size of the stones (one on each side) and the enormous hydronephrotic distention made it seem impossible that the stones were responsible for the latter condition. The etiologic cause of the stones was to be sought rather in the presence of the polar vessels, a congenital anomaly; the pathologic changes, then, were the result and not the cause of the lesion. The bilateral changes pointed definitely to this conclusion.

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[24] Astraldi, A., and Repetto, R. L.: Hydronéphrose double par vaisseaux polaires inférieurs avec calculose bilatérale, Arch. d. mal. d. reins **10**:255-257 (May) 1936.

Therapy naturally had to consist of both medical and surgical procedures and should include treatment of focal infection, local treatment of renal infection, surgical extraction of the calculi, postoperative treatment of the septic foci to prevent the recurrence of calculi and. finally, reduction of the hydronephrosis by section of the polar veins. Retention and infection both had to be taken into account. There was a vicious circle. The retention could not be definitely overcome before operation, as the lesion was congenital and its cause (the polar veins) still existed. While the infection might have been improved, one could not hope to get rid of it altogether while the retention persisted. But the age of the patient and the apparent size of the calculi, as well as the results of the tests of renal function, all indicated operation. The two kidneys were operated on; the interval between the operations was forty-five days. In each instance the polar vessel was sectioned, and a single calculus was removed by inferior pyelotomy. On the basis of their experience in this and other cases, the authors were convinced that in cases in which there is pyelitic dilatation the use of an indwelling catheter after pyelotomy retards cicatrization rather than hastens it as it does in cases in which there is neither dilatation nor retention. The wounds in this case seemingly would not close until the catheter was withdrawn.

In view of the great size of the hydronephrosis, it was not to be expected that there would be any material reduction in the size of the pyelitic sac, and a roentgenogram made ten months after operation confirmed this assumption. The urine still contained staphylococci and pus. A small calculus, the size of a hazelnut, had been eliminated shortly before the report was written, despite the multiplicity of methods employed to combat infection. Postoperative treatment included use of indwelling catheters, lavage of the renal pelvis, administration of vaccines and extirpation of septic foci. It appears to be impossible to acidify the urine, although an attempt is being made to accomplish this by means of a ketogenic diet.

Denervation.—Schneider and Wildbolz,[25] in an effort to elucidate the changes induced by denervation of the kidney and therefore to make the indications for this operation more definite, studied the flow of blood of the normal and of the denervated kidney in dogs. The method used was the thermostromuhr method of Rein. By this method it is possible to measure the flow of blood of unopened blood vessels in situ; in this case the flow in the renal artery and vein was observed under physiologic conditions. The authors found that the normal flow of blood is from 80 to 180 cc. per minute through one kidney of a dog weighing from 9 to 29 Kg., that is, from 4 to 10 cc. per kilogram of body weight. It averages from 1 to 2 cc. per gram of kidney per minute. After they established and registered the normal flow of blood for several hours, the kidney was denervated. For purposes of denervation, both the artery and the vein were carefully freed of visible nerve fibers; chemical sympathectomy was not performed, and the ureter was left intact. The result of this procedure was in all experiments the same. First, they noted a short period of contracture of the blood vessels and the diminished flow of blood followed by a period of unstability and then an increase in the flow; two hours later the flow of blood had risen to 165 to 245 per cent of the original flow. When, at that moment, decapsulation was carried out, the flow of blood increased 20 per cent, probably because of mechanical factors. Decapsulation alone, without denervation, caused a 20 per cent increase in the rate of the flow of blood. The reason for this could not be determined. The most interesting part of the study, however, is the part in which the authors proved beyond doubt that by the simple operative method used the kidney was totally denervated. To prove this they subjected the animal to different well established reactions. The principal one was artificial respiration with air which had a high carbonic acid content. Fleisch has proved by accurate experiments that a rise in the carbon acid content in the blood produces a rise in the flow of blood in denervated regions by dilatation of the blood vessels. Rein was able to show that the contrary was true in regions in which the nerves were intact through vasoconstriction by way of the vasomotor nerve center. Schneider and Wildbolz found that the normal kidney reacted to a high carbonic acid content in the blood by a marked diminution in the flow, notwithstanding a rise in the blood pressure. The contrary was true in a denervated kidney; a high carbonic acid content in the blood was the cause of a marked rise in the flow of blood. Decapsulation alone did not change the reactions of the kidney. In the other physiologic tests used, the carotid sinus reflex and the reaction to intravenous injection of epinephrine indicated similar although less clear results.

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[25] Schneider, Max, and Wildbolz, Egon: Dekapsulation und Enervation der Niere und Nierendurchblutung, Ztschr. f. urol. Chir. u. Gynäk. 43:1-12 (Feb.) 1937.

Nephrofibrosis.—Cumming and Schroeder[26] reviewed 15 cases of renal atrophy and sclerosis and named the condition "nephrofibrosis." They expressed the opinion that even though the lesion in the diseased (atrophic) kidney appears to indicate an old infarct the involvement actually may be the result of ascending infection associated with pyelonephritis, vascular changes and limitation of the nephrofibrotic areas, which correspond to the units supplied by those particular vessels which are end-arteries and have no anastomosis proximal to the glomeruli they supply.

Hinman's theory of counterbalance explains many failures in operations, such as those on advanced hydronephrotic kidneys; yet, as Abeshouse said, if this theory were applied to all clinical cases of unilateral surgical diseases of the kidney in which there are varying degrees of destruction of parenchyma on the involved side, it would seem futile to attempt such procedures as plastic operations for hydronephrosis, pyelolithotomy, nephrolithotomy and renal resection.

One reasonable basis for acquired atrophy and nephrofibrosis is that the peculiar renal status develops as a negative response to natural need; if one kidney has long carried the load of renal function, its fellow gets no biologic urge until sufficient disorder occurs to prevent appreciable recovery. The mechanism of this phenomenon may be a gradual lessening of the blood supply and consequent degenerative vascular changes which prohibit a retro-active improvement.

The authors' interest in this subject has been stimulated by the observation that without anticipated or logical reason certain kidneys simply refuse to function after apparently successful and routine operative intervention. This startling condition often goes unrecognized; the patient and the surgeon remain blissfully ignorant of it until some circumstance brings a wary roentgenologist to recognize rank loss in functional activity, a small renal shadow and contralateral hypertrophy of a kidney, or until the interested surgeon finds, to his chagrin, that the operation has rendered the kidney entirely useless.

Trauma.—Wood,[27] during the period from 1929 to 1935, has treated 25 patients who had an injured kidney. Seven of these were children, 18 were adults, 24 were males and 1 was a female. In 11 cases the right kidney was injured, and in 14 cases the left kidney was injured. Eleven kidneys were ruptured, 2 were lacerated and 12 were contused. Ten injuries were caused by automobile accidents, 8 injuries occurred while the patients were engaged in athletics, 4 injuries were caused by horses and 3 injuries were due to industrial accidents.

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[26] Cumming, R. E., and Schroeder, C. F.: Renal Atrophy, J. Urol. **37**:407-436 (April) 1937.

[27] Wood, A. H.: Diagnosis and Treatment of Trauma to the Kidney, J. Urol. **37**:437-465 (April) 1937.

Excretory urography was employed in 17 cases, and satisfactory roentgenograms were obtained in all instances on the uninjured side and in 12 cases on the injured side. In 3 cases rupture of the kidney was clearly demonstrated. In the 5 cases in which the roentgenograms were not satisfactory on the injured side, 2 patients required nephrectomy and 3 recovered without operative intervention. In 1 case there was extravasation of the opaque solution into the lower pole of the kidney, and four months later a phenolsulfonphthalein test revealed a 60 per cent decrease in function. Retrograde pyelography was employed in 2 cases. Operation was performed in 13 cases; nephrectomy was done in 10 cases, suture and drainage in 2 cases and exploration and drainage in 1 case.

In these 25 cases there were 3 deaths. Two deaths occurred after operation; one of these was due to an injury of the head and the other to postoperative pneumonia. The third death was due to unrecognized rupture of the kidney and injury to the peritoneum and the mesentery, which were determined at necropsy.

Perinephric Abscess.—Nesbit and Keene[28] discussed perinephric abscess which was associated with bronchial fistula. Sixty cases of perinephric abscess were studied. The average age of the patients was 31 years; the youngest patient was 2 years of age, and the oldest patient was 69. Forty-two per cent were between 20 and 40 years of age. Forty patients, or 66 per cent, were males. The left side was involved 32 times and the right side 27 times. One patient had bilateral abscesses. The average duration of localizing symptoms was three months. Thirty-five patients, or 58 per cent, had had symptoms for one month or less. The longest duration was twenty-two months, and the shortest was one day. The operative mortality was 2 per cent. The total mortality, operative and nonoperative, was 25 per cent. Eleven types of bacterial etiology were found. In 20, or one third, of the 60 cases, the condition was correctly diagnosed within three days after the admission of the patient to the hospital or within three days after the development of symptoms, while the patient was undergoing treatment for some other condition. In 6 cases, or 10 per cent, a perinephrobronchial fistula was present; that is, pus from a perinephric abscess had drained through the diaphragm, pleura and parenchyma of the lung and into a branch of the tracheobronchial tree.

A comparison of the cases in which bronchial fistula developed and the other cases in the series reveals one significant fact: The average duration of localizing symptoms was eight months in the cases in which a fistula developed and three months or less in the uncomplicated cases. Nesbit and Keene were of the opinion that involvement of the diaphragm, pleurae and pulmonary parenchyma is a common sequel of chronic perinephric abscess but may not be recognized as such. This is well illustrated in one of their cases in which operation was postponed because of coarse râles and dulness over the base of the homolateral lung, which were interpreted as signs of pneumonia. Analysis of the chain of cause and effect in this condition brought them to the conclusion that the only preventive measure is early establishment of a primary diagnosis of perinephric abscess.

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[28] Nesbit, R. M., and Keene, C. H.: Perinephric Abscess with Bronchial Fistula, J. Urol. **37**:695-705 (May) 1937.

When the diaphragm is involved in a penetrating suppurative process from below, the formation of an adhesive pleuritis at the site of penetration prepares the way for a bronchial fistula. In the absence of adhesion between the visceral and the parietal pleura, empyema results. Treatment of perinephric abscess associated with bronchial fistula is the same as for the uncomplicated abscess. Incision and drainage suffice also for the pulmonary sequelae. Resolution of fever is concomitant with the decrease in sputum. However, if empyema develops, drainage of the pleural cavity is imperative.

Infection.—In the communication by Cabot [29] only blood-borne infections of the kidney were considered, and chiefly those produced by the pus-producing cocci. For many years it has been known that various of these cocci may be found in otherwise normal urine of a patient who has a peripheral infection, such as a boil, a carbuncle, a septic wound or an acute infection of the upper part of the respiratory tract. In order to investigate the latter point more closely, a series of 46 patients who had an acute inflammatory process about the mouth, throat or ear were studied. The group was selected from among patients who had urine normal to ordinary tests and some fever but no signs or symptoms suggesting an infection of the kidney. The urine was carefully obtained, always by catheter from the females. It was studied by smear and culture, the smear being made from urine centrifugated for a considerable period at high speed. Organisms were found in the smear in 32 cases and in the culture in 18 cases.

In a group of 10 apparently normal persons who were used as controls, the smear did not contain any organisms, but in 2 there was a positive culture of streptococci.

It is important to note that the pus-producing cocci appear in the urine early in the disease; they disappear as a rule in a few days, although they occasionally persist for several weeks in an otherwise normal urine.

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[29] Cabot, Hugh: Blood Stream-Infections of the Kidney, Brit. J. Urol. 8:233-256 (Sept.) 1936.

The lesions are primarily cortical and medullary. They tend to coalesce with the production of massive abscess, usually show early and marked perinephritis and often result in a perinephric abscess.

Besides the classic methods of diagnosis, stress was laid on the value of roentgenography in the diagnosis of these cases. Clouding or obliteration of the shadow of the psoas muscle is generally discoverable by modern methods in cases of perinephric abscess. Scoliosis is not rare, but is a rather late sign. Limitation of the motion of the diaphragm on the infected side, as studied by the roentgenoscope, is more important than the literature would suggest. Particular emphasis was laid on the value of pyelography both by the excretory and the retrograde method. This will give precise information as to the development of massive abscess by showing deformities of the calices. It will also be of much value in showing displacement of the kidney by perinephric abscess, sometimes at an early period. Stress was laid on the value of limitation of the normal mobility of the kidney due to the early development of perinephritis, often in the absence of perinephric abscess. A series of observations showed diminished visualization of the infected kidney as seen in the excretory urogram. Further study will be necessary to evaluate this sign, since it may be produced either by diminution of the function of the kidney or by the obscuring of the shadow of the renal pelvis by overlying inflammatory tissue.

For the purpose of treatment the cases were divided into four groups. Operation is believed to be the only available method of treatment in cases of fulminating infection.

In cases of acute infection the condition is characterized by chills, high fever, leukocytosis and costomuscular tenderness associated with urine that is normal except for the practically universal presence of cocci obtained by staining the sediment after prolonged centrifugation at high speed. In these cases operation has been generally regarded as almost invariably necessary. The author disagreed with this opinion and stated that in a majority of such cases recovery will take place under medical treatment. A position of "armed watchfulness" should always be maintained, and one should carefully observe the reaction of the patient to the disease, particularly as regards the tendency of the pulse to become more rapid and for anemia to develop. Coupled with this should be frequent observations of the conformation of the renal pelvis both by excretory and by retrograde pyelography. This will enable massive abscess and perinephric abscess to be discovered early.

The third group includes cases of subacute infection in which the picture is less stormy but in which there is clear evidence of a lesion of the kidney. In these cases operation is not indicated unless perinephric abscess develops.

The fourth group consists of borderline cases in which the condition occurs not rarely as a complication of infection of the upper respiratory passages. The diagnosis can be made only on the basis of slight costomuscular tenderness, fever which is not satisfactorily accounted for by the conditions in the throat and by the finding of cocci in the urine. In these cases operation is practically never necessary, since perinephric abscess is very uncommon.

Indications for operation are: (1) the fulminating type of infection; (2) the widespread infection of the kidney with which the patient seems unable to control the disease, as shown by the development of anemia and failing general conditions; (3) massive abscess of the kidney, as shown by the pyelogram, and (4) perinephric abscess.

The types of operation indicated are: (1) nephrectomy in cases of fulminating infection; (2) nephrectomy for widespread infection without massive abscess, when the patient is losing ground; (3) decapsulation and drainage for a massive abscess which is well localized, and (4) exploration for perinephric abscess. The precise operation is determined by the following factors: (*a*) If the pyelogram shows no evidence of massive abscess or evidence of deformity of the pelvis, simple drainage should be employed; (*b*) if there is perinephric abscess and evidence of massive abscess, the perinephric abscess must be drained and the kidney explored in the region indicated by the pyelogram, and (*c*) if there is perinephric abscess of long standing, even with evidence of destruction of renal tissue as shown by the pyelogram, drainage of the abscess alone is indicated in the first instance. Many of the patients with long-standing abscess will then recover, since the massive destruction of the kidney has already drained into the perinephric space. It is not wise to uncover the kidney widely in such cases, since extensive dissection will be necessary with the breaking down of well established barriers. If after the perinephric abscess has been drained the wound fails to heal, or if it reopens after healing, further exploration can be safely undertaken.

URETER

Anomalies.—Campbell[30] reported 17 cases of ectopic orifice of the ureter; the patients were infants and children. Nine of the patients were examined urologically, and in 7 cases the orifice was seen. Persistent pyuria was the indication for urologic investigation in these 7 cases.

Ectopic orifice of the ureter occurs twice as frequently in females as it does in males. In this series of cases, the anomaly occurred on the left side in 11 cases, on the right side in 4 cases and on both sides in 2 cases.

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30. Campbell, M. F.: Ectopic Ureteral Orifice: A Report of Seventeen Cases in Children, Surg., Gynec. & Obst. **64**:22-29 (Jan.) 1937.

The urinary tract above the ectopic orifice is dilated as a rule. The orifice, however, is usually large, so that urinary obstruction and back pressure are not commonly factors in producing the dilatation. In most cases of ectopic ureter a normal urinary schedule is accompanied by a constant urinary dribbling. This indicates that the external sphincter is inadequate or that the ectopic opening is peripheral to the sphincter. Children as well as adults who have this condition are often treated for enuresis. In cases in which the urinary control is normal, a condition which is less common, the orifice opens behind a competent sphincter. The persistence of disturbances of micturition or of pyuria in either a child or an adult requires a thorough urologic examination. Excretory urography may yield a suggestive clue when ureteral reduplication is revealed, but two isolateral orifices are not found in the bladder, and retrograde pyelography proves that incomplete ureteral reduplication does not exist.

If the ectopic ureter is the only one for the kidney, transplantation to the bladder is indicated in the absence of marked infection. In the presence of significant infection of the anomalous segment and if the condition of the opposite kidneys permits, ureteronephrectomy is the usual indication. If the opening of the ectopic ureter is from one of two reduplicated ureters and only the ectopic segment is diseased, ureteroheminephrectomy should be carried out. If both renal segments are diseased and the opposite kidney is adequate, nephrectomy is the treatment of choice. When nephrectomy alone would leave a large dilated ureter, ureteronephrectomy should be performed. In Campbell's series of cases, ureteroheminephrectomy was done five times, ureteronephrectomy and bilateral ureterostomy each was done once and operation was refused once. The youngest patient to undergo renal resection was 6 months of age. All the patients survived. Four were known to be bacteriologically cured. In another case in which a child was temporarily cured, reinfection subsequently occurred. Two years later, fibrosarcoma of the scapula developed.

Extravesical ureteral openings are reported relatively seldom in the literature. Both sexes are affected, but the condition is usually symptomless when it affects the male. McKirdie and Polkey[31] reported a case in which a ureter opened into the seminal vesicle, and they gave a gross and microscopic description of the specimen. Nineteen similar reports have been found in the literature; these were briefly summarized. A brief résumé of the embryology and a discussion of the accepted theory of causation of the malformation were presented.

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[31] McKirdie, Matthew, and Polkey, H. J.: Extravesical Ureteral Opening into the Seminal Vesicle, J. Urol. **37**:706-714 (May) 1937.

Furniss[32] reviewed the reported cases of supernumerary ureter which was associated with an extravesical opening.

In Thom's classification, the most complete of the reviewed published articles, there were 185 cases, 63 being in males and 117 in females; in 5 cases the sex was not mentioned. The supernumerary ureters were on the right side in 82 cases and on the left side in 73 cases; no information regarding the side was given in 22 cases. There were 58 cases of single ureter with extravesical opening, 6 cases of bilateral single ureter with extravesical orifice, 96 cases of unilateral duplication with extravesical opening of accessory ureter, 2 cases of complete duplication of the ureter on one side with extravesical opening of both ureters, 21 cases of bilateral complete duplication with extravesical opening of only one ureter and 2 cases of bilateral duplication of the ureter with extravesical opening of all ureters. In the male patients, the opening was found in the prostatic urethra 33 times, in the seminal vesicles 17 times, in the vas deferens 6 times and in the ejaculatory ducts 5 times. In the female patients, the opening was found in the urethra 37 times, in the vagina 32 times, in the uterus 3 times and in the vestibule 45 times.

Among the females, a history of incontinence since birth was usual. The urethral orifice may have been situated so near the bladder that the urine was returned to the bladder in the waking state and leaked when the child was relaxed in sleep. At times pyuria, for which no satisfactory explanation can be found either in the bladder or in the kidneys the ureters of which drain into the bladder, is the only sign. In some cases fever, without any localizing signs, or pain in the region of the kidneys may be the only expression of the trouble. Intravenous urograms are of value if there is enough functioning tissue in the upper part of the kidney to eliminate the contrast medium, a condition seldom found. Indirectly, they may help if they show absence of the normally visualized upper calix of the kidney and if above this there is a shadow of more kidney tissue than one ordinarily would find with a single renal pelvis. Occasionally, the dilated accessory ureter can be seen cystoscopically, when the ureters run rather superficially under the vesical mucosa. In some instances the dilated ureter has been noted by palpation and inspection on the under surface of the urethra.

Many treatments have been devised. These include ligating the ureter, anastomosing it into the bladder or intestine, uniting the pelves of the two portions of the kidney, heminephrectomy and nephrectomy. Before instituting any plan, the following facts should be determined: the amount of renal tissue drained by the accessory ureter, the degree of distention of the ureter and pelvis, the function of the portions of the kidney and of the opposite kidney and whether or not there is infection. Furniss expressed the belief that any form of simple ligation should be abandoned. Anastomosis to the bladder should be done only when the ureter is that of a solitary kidney or is the only ureter draining one of a pair of kidneys, or in cases in which a single ectopic ureter drains both kidneys or in which one of a pair of ureters drains a worth-while portion of a kidney in which there is little, if any, infection. Furniss stated that the best and most satisfactory method is heminephrectomy. This usually can be done rather easily. The upper and lower poles nearly always have an independent blood supply; the upper pole is most often demarcated from the lower pole, and the separation can be made with a minimal loss of blood. Even when the two portions appear to be intimately blended, the upper can be cut away with the electric cutting instrument. Individual bleeding points can be caught with the forceps and ligated or electrocoagulated. A technical point of advantage is to strip the capsule from the upper pole toward the lower pole before resection. This helps in closing the wound in the upper pole. If there is oozing, fat or, even better, muscle tissue can be placed in the wound and the capsule sutured over it.

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[32] Furniss, H. D.: Supernumerary Ureters with Extravesical Openings, J. Urol. **37**:341-357 (March) 1937.

Stone.—Moore [33] discussed the factors which determine the management of ureteral stones and described an improved method for their cystoscopic removal.

The larger the stone, the less likely are manipulative efforts to succeed. If the calculus is more than 1 cm. in diameter and if it seems probable that more than three cystoscopic treatments or ureteral dilations will be required before the stone can be recovered, it is often less trying on the patient and possibly less hazardous, to proceed immediately with an extraperitoneal ureterolithotomy. A stone impacted in the lower third of the ureter is decidedly more amenable to manipulative removal; if it is lodged in the upper or middle third and is not more than 1 cm. in diameter, one may await its passage into the more favorable pelvic portion. In the case of larger stones, lumbar ureterotomy should be more frequently employed. One hundred and thirteen cases form the basis of this report. In 20 cases the stone was lodged in the upper part of the ureter; in 13 of these cases cystoscopic treatment was not attempted; of the 6 cases in which manipulation was tried the results were successful in only 2. Seventeen patients were subjected to lumbar ureterolithotomy, and 1 patient passed a small stone spontaneously after cystoscopic examination. On the other hand, of 100 stones lodged in the lower portion of the ureter, 14 were passed spontaneously after the examination. Of the remaining 86 patients, 77 were subjected to cystoscopic treatments, and 64 stones were recovered. Surgical intervention became necessary in 13 cases after manipulation failed; ureterolithotomy was performed in 6 cases, without previous efforts to remove the stone instrumentally; in 3 cases a nephro-ureterectomy was performed because of complete renal atrophy which was secondary to a long-standing obstruction due to calculus.

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[33] Moore, T. D.: Factors Determining the Management of Ureteral Stones: An Improved Method of Their Cystoscopic Removal, J. Urol. **37**:1-11 (Jan.) 1937.

Duration of symptoms always merits consideration; if the onset is recent, expectant treatment for a few days may be followed by the spontaneous passage of a stone. If there is a history of attacks of renal colic occurring over a period of weeks or months, it is obvious that the assistance of the urologist will be necessary.

Urinary stasis of varying degrees is a feature demanding special consideration in many cases and is most safely demonstrated by excretory urography. Stasis must be recognized as fertile soil for infection; it occasionally prohibits the employment of manipulative methods. The function of the involved kidney is of importance. In this regard an excretory urogram may be misleading; temporary or reflex inhibition of function, with absence of the medium on the affected side, is of frequent occurrence in the presence of ureteral stone. In a recent study of 150 urograms there were 11 in which one or more stones in the ureter caused absence of function which was temporary, as proved by return to normal function after removal of the calculi. If no function is demonstrable either by urography or by the dye tests, nephrectomy may be indicated.

Females withstand manipulation better than males. If multiple catheters are used, more of them may be passed at one sitting by reintroducing the cystoscope alongside catheters previously inserted. On women, vaginal ureterolithotomy may also be employed advantageously. Elderly and enfeebled patients require the most gentle treatment possible and should not be subjected to a long series of instrumentations; only when the stone is small and unquestionably favorable for manipulative removal should this type of treatment be instituted. In infants and children ureteral stones fortunately are comparatively rare and are usually of small size. The mere passage of a catheter may bring about expulsion of the stone. In this series of 113 patients the only death was that of a man aged 70, whose general condition was unfavorable for any type of treatment. He was obese and had diabetes, hypertension and chronic myocardial degeneration.

McKay described an ingenious dislodger, embodying the principle of multiple catheters but using, instead, four long silk threads attached to a small bougie (no. 3 French) of whalebone. He suggested that it be passed beyond the stone, after the ureter was thoroughly dilated, and by pulling on the threads and holding the filiform bougie firmly it would become slightly bowed: the stone would become entrapped by twisting and could be brought down into the bladder by traction. After Moore had tried this technic in a few cases with indifferent success, it occurred to him that this device might be used to a better advantage by passing the filiform which carried the threads well beyond the stone, even as far as the renal pelvis, and then withdrawing it by traction only, with no effort to induce bowing. The obstructing stone causes the threads to wad above it and form a small mass, which does not easily permit the point of attachment of the threads to be withdrawn unless the stone also is brought along. If a calculus is engaged in this way and does not slip out easily by steady or intermittent traction, or if for any reason one desires to abandon the effort, the bougie may be inserted further and the strands of thread may be easily drawn out along with the filiform. Since the author has used this technic there have been no accidents, embarrassing experiences or apprehensive moments. It cannot be overemphasized that the ureter should be dilated well before insertion of the dislodger. A direct cystoscope of the Braasch type is preferred, as the catheter guide of this instrument renders unnecessary the passage of the bougie through a length of catheter; moreover, there is no deflector to become entangled with the threads.

This method has been used in a group of 31 cases, in which there were 33 ureteral stones to be removed. Twenty-four stones were removed on the cystoscopic table. Twelve stones were removed at the first treatment; 7 required two treatments, 4 required three treatments and one required four treatments, making a total of forty-two treatments, or an average of one and three-fourths for each stone. When more than one cystoscopy was necessary, an interval of from five to ten days was customary, with gradually increasing dilation of the ureter as a preliminary measure. A few cubic centimeters of sterile oil should be injected before the dislodger is passed.

Transplantation.—Hinman and Weyrauch [34] said that a study of the literature on uretero-intestinal implantation leaves one with a feeling of disappointment at the lack of improvement with the advent of newer methods and greater experience. It would seem that every surgical principle imaginable has been tried. Of the 11 listed by Hinman and Weyrauch in their study, the submucosal principle has a distinct advantage in theory and has shown the best results in practice. Nearly all modern technics make use of it, either as the primary or as the secondary principle. Even the newest methods which utilize the intact ureter with the idea of asepsis are primarily submucosal. The problem of the formation of an opening between the ureter and the bowel at the second stage of the operation, by methods based on the eleventh principle, has not been satisfactorily solved. The final test of a successful implantation is not only recovery from the operation but survival with normal ureters and kidneys. The lateral opening of those technics using it is unsatisfactory because of its tendency to constrict and produce obstruction. In practice, the advantage gained by the healing of the ureter in its intestinal channel under conditions of asepsis is offset by the difficulties of establishing a full opening afterward. Simpler one stage methods which give an orifice at the end of the ureter may prove superior.

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[34] Hinman, Frank, and Weyrauch, H. M., Jr.: A Critical Study of the Different Principles of Surgery Which Have Been Used in Uretero-Intestinal Implantation, Tr. Am. A. Genito-Urin. Surgeons 29:15-156 (May) 1936.

In addition to these elementary principles representing the 11 major differences in technic, several conditions must be recognized as common to all technics, no matter how elementary or compound. These are the basic principles of intestinal and ureteral surgical procedures and must be fulfilled by any method. What produces localized necrosis of the intestine or perforation and tearing out of sutures, the common causes of postoperative leakage and peritonitis? What produces the constriction which leads to intestinal obstruction? Why is anemic infarction, extensive necrosis, diffuse ureteritis or marked dilatation of the ureter seen at necropsy? Too often the answer is failure to follow the simple well known rules for intestinal and ureteral surgical procedures. The only layers which are safe for suturing are the submucosal layer of the bowel and the adventitia of the ureter. Sutures cannot penetrate the lumen of either without danger. Their blood supply cannot be disturbed to any great extent. Neither one can be unduly traumatized, twisted or displaced. These are some of the basic principles that must be followed.

The marked difference between the risk of implantation for exstrophy (less than 15 per cent) and that for cancer (almost 50 per cent) arises partly from differences in the age period but mostly from the added risk of the operation for the malignant condition. Statistics also show that implantation in two stages (one ureter at each), as done for most exstrophies, is safer than simultaneous bilateral implantation. The latter is the usual method used for malignant conditions, because of the necessity for a second operation to remove the cancer. Perfection of the principle of the intact ureter to a one stage operation or the development of any safe procedure in one stage will lower the mortality of cystectomy for malignant conditions. Until such a procedure is developed, the implantation of the second ureter at the time of cystectomy is the safest plan.

The theoretical advantage of extraperitoneal operations has not proved to be practical. Peritonitis results from leakage after operation and not from contamination at the time. When sutures are placed properly, leakage does not occur. The little protection against leakage gained by extraperitoneal exposure is more than offset by the increased difficulty of implanting the ureter untwisted, unkinked and unobstructed.

Finally, it appears from this study that the problem remains unsolved, and one must recognize that the problem involved is not solely one of surgical technic. There is the unknown, indeterminate but ever present factor of urinary sepsis. Susceptibility to infection varies with persons as does the conjunction at operation of accessory and other factors which favor it. Varying degrees of pyelonephritis and infected hydronephrosis often are present already, and experience shows that such conditions are rather favorable than otherwise when they have led to a well established immunity. Whether the tract above is clean or not, there is the chance that an acute infection will ascend from the bowel to the kidneys as soon as a communication is established. The surgeon who knows the individualistic, technical and bacteriologic factors of success and failure is in a position to reduce the uncertainty of the operation to a minimum. The success of the future may lie along lines of immunity as much as of technic.

Higgins[35] stated that in a series of 78 cases in which transplantation of the ureters into the rectosigmoid was performed, the best results were obtained when the following principles were carried out: In cases in which cystectomy and transplantation are performed for carcinoma of the bladder (modified for children requiring a similar operation), a liquid, nonresidue diet is supplemented by dextrose, candy and gelatin. One thousand cubic centimeters of a 10 per cent solution of dextrose is given intravenously each day. Dextrose is administered in physiologic solution of sodium chloride if the renal function is not impaired; if the function is decreased, dextrose is given in distilled water. Magnesium sulfate is given daily by mouth. One ounce (32 Gm.) of magnesium sulfate is dissolved in 8 ounces (240 cc.) of water, and 1 ounce (30 cc.) of this mixture is given every half-hour, starting at 7 a. m. No magnesium sulfate is given on the day prior to operation. Daily cleansing enemas are given until they return clear. These are given in the afternoon. Two drachms (8 cc.) of camphorated tincture of opium U. S. P. is given at two hour intervals for three doses—usually at 4, 6 and 8 p. m. —the night before operation.

The type of operation to be performed is influenced by the judgment of the surgeon and his familiarity with the various operative procedures. Certainly the operation which is attended by the lowest mortality and morbidity in his hands should be employed.

After operation the patient is maintained in a flat position for eight hours if spinal anesthesia has been employed; then Fowler's position is used. After spinal anesthesia the blood pressure is checked every fifteen minutes until it returns to normal. No food or water is given by mouth for at least forty-eight hours; then small amounts of water are given by mouth for twelve hours. During the following twelve hours administration of clear fluids is started; 1 ounce (30 cc.) is given hourly, and this amount is gradually increased. A low residue diet is then used for from five to seven days. The fluid intake is kept at 3,000 cc. daily. During the first two days, 2,000 cc. of a 10 per cent solution of dextrose is given intravenously and an infusion of 1,000 cc. of saline solution is given daily. After this, fluids are given intravenously, as indicated by the chemical composition of the blood and by the fluid intake by mouth. Narcotics are prescribed as necessary. A rectal tube is inserted at the time of operation. This may be changed but is replaced and left in the rectum from eight to ten days. The rectal tube is gently irrigated with physiologic solution of sodium chloride at intervals of two hours to insure patency. If the transfixion suture technic is employed, gentle traction is made on the rectal tube at the end of twenty-four and of thirty-six hours or until the tube containing the suture is expelled. A plain rectal tube then is reinserted for from five to seven days. The composition of the blood is studied daily. Ten cubic centimeters of methenamine-acetylaminosalicylic acid is given with the dextrose as a urinary antiseptic, for the first three or four postoperative days.

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[35] Higgins, C. C.: Transplantation of the Ureters into the Rectosigmoid: An Experimental and Clinical Consideration, J. Urol. **37**:90-105 (Jan.) 1937.

The patients who have benign conditions and who survive the operation—and the ratio of these patients is steadily increasing—may be expected to live an indefinite period. Higgins has seen patients who are living and in good physical condition after eighteen, sixteen and fourteen years, respectively. It is yet too soon to know what the results may be in cases in which patients have been operated on for malignant conditions, but Higgins was certain that it will be possible to salvage a fair percentage of these unfortunate persons who are destined to a miserable end from malignant tumors of the urinary bladder.

Drainage.—Foulds.[36] stated that prolonged drainage of the lower part of the urinary tract has long been accepted as a valuable procedure in obstruction of the lower part of the urinary tract. Drainage of the kidney by nephrostomy after the removal of renal calculi is advisable in certain cases as a means of promoting better function and decreasing infection. The use of the indwelling ureteral catheter is recognized in the treatment of pyelitis of pregnancy and other infections of the upper part of the urinary tract. In cases of impacted stones in the ureter and infection in the kidney and dilatation of the ureter, temporary ureterostomy with a T tube offers a means of providing sufficiently prolonged drainage of the ureter to allow improvement in renal function to occur and renal infection to subside. The T tube is of use in the reconstruction of the ureter after operation for impassable stricture.

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[36] Foulds, G. S.: Prolonged Drainage of the Ureter, Tr. Am. A. Genito-Urin. Surgeons **29**:1-5 (May) 1936.

Di Maio,[37] on the basis of a special study of 68 cases in which the indwelling ureteral catheter was used, concluded that there are practically no contraindications to its use and that the method not only gives symptomatic relief but conduces to cure in various pathologic conditions of the urinary system. By analyzing his results according to the type of case, he reached the following conclusions:

For ureteropyelitis from various causes (movable kidney, ureteral stone expelled without operative measures), when there is still sufficient tonus of the pelvis and the ureter, endoscopic ureteral drainage results in rapid and certain cure. In cases of abscessed kidney which is not easily distinguished from simple pyelitis, the negative action of this drainage constitutes a means of differential diagnosis, on the basis of which it is possible before the condition becomes too grave to do a conservative operation (decapsulation or lumbar drainage), which can be followed by a radical procedure at a later time. In cases of movable kidney, the hematuria of hydronephrosis ceases with the placing of an indwelling catheter. In cases of pyelitis associated with pyonephrosis of the other kidney and in mild hydronephrosis of one kidney with grave hydronephrosis of the other kidney, ureteropyelic drainage of one or both sides improves the general condition and by curing the pyelitis or improving the mild hydronephrosis makes it possible later to carry out a radical operation on the other side. In cases of hydro-ureteropyonephrosis from ureteral calculus, such drainage (when it can be accomplished) reduces the septic condition and favors a normal postoperative course. Even with inoperable conditions, such as bilateral calculous hydropyonephrosis, it makes some improvement possible, as it does also with hydropyo-ureteronephrosis of gynecologic origin, for which operation is contraindicated.

Even when such drainage is maintained with the same catheter for one to seven days and repeated several times and for many months, it is impossible to establish precise limits or contraindications to its use, since it is possible to apply conservative drainage even in the presence of grave suppurative and inoperable conditions, for the relief it brings. With less severe inflammatory processes of the ureter and pelvis, this drainage can be applied when other common measures are shown to be inefficacious.

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[37] di Maio, Giorgio: Il drenaggio uretero-pielico endoscopico in alcune affezioni chirurgische settiche uretero-pielo-renali, Arch. ital. di urol. **13:**391-424 (July) 1936.

(To be concluded)

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INFLUENCE OF VENOUS STASIS ON THE PRODUCTION OF CHRONIC ARTHRITIS

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LOS ANGELES

Circulatory disturbances resulting from either experimentally produced venous stasis or obstruction of the arterial blood supply have been claimed to produce the changes of chronic arthritis. If venous stasis or passive congestion is capable of producing chronic arthritis, then the joints of the ankles and feet of persons with long-standing edema and stasis from varicose veins of the legs should show evidence of arthritis. In an effort to determine what effect if any venous stasis has clinically on the production of chronic arthritis, thirty cases of varicose veins of long standing in which definite and prolonged edema of the ankles and feet had existed were studied.

The patients in this group of cases presented histories of long-standing varicose veins of the legs with marked congestion of the ankles and feet associated with edema, cyanosis and occasionally eczematous changes of the skin, such as scaling and brownish discolorations. A palpable decrease in the cutaneous temperature of the feet was often present, and arterial pulsation of the dorsalis pedis and posterior tibial arteries was frequently diminished and in two cases was not obtainable. Some of the patients had ulcers of the legs of varying duration associated with the varicosities. The Wassermann reaction of the blood was negative in the cases in which ulceration was present.

Roentgenograms were made of the legs and feet. These were studied for signs of chronic arthritis, such as capsular thickening, marginal articular lipping, narrowing of the articular cartilage and subchondral sclerosis, and also for periosteal new bone formation of the tibia and fibula, especially in the cases of ulceration.

To be certain that the venous stasis did not merely involve the superficial soft parts without similarly affecting the deeper periarticular structures, tissue surrounding and including the joint capsules of the ankles and feet was obtained at autopsy in three cases of long-standing

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stasis associated with varicose veins. On gross examination this tissue appeared thickened, as from edema, and microscopically revealed evidence of edema, arterial thickening with some thrombosis and an increase in fibrosis.

Of the thirty patients studied, twenty-one were men and nine were women. The ages ranged from 29 to 83. Varicose veins had existed for from one to fifty years. Eighteen patients had either old healed varicose ulcers or ulcerous lesions on the legs when studied. There were five cases in which hypertrophic arthritis of joints other than those of the foot and ankle was demonstrated.

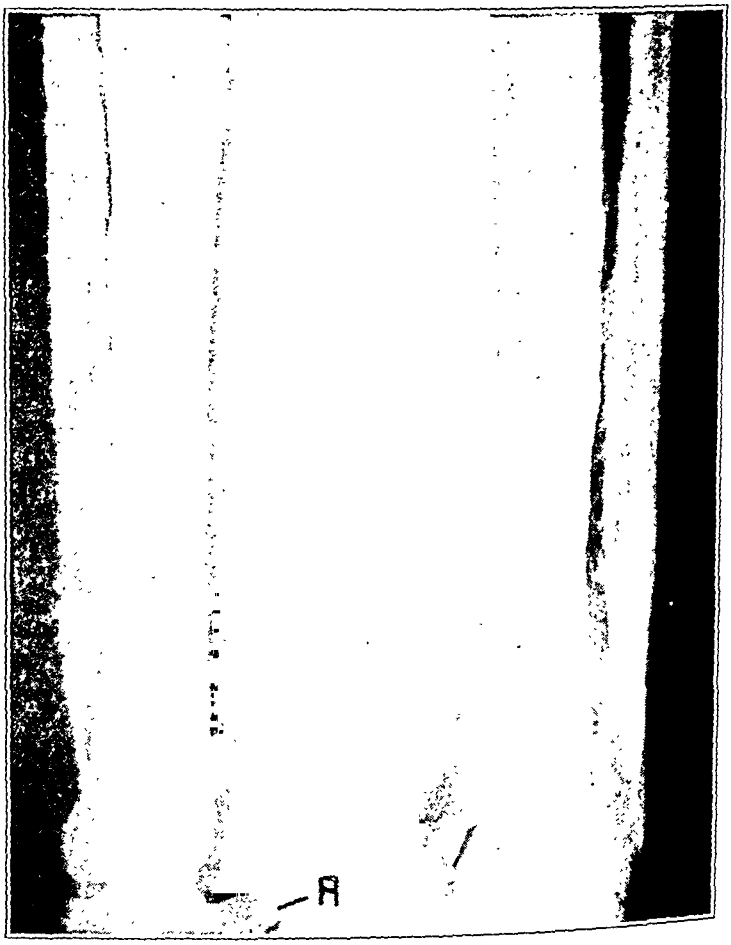

Fig. 1 (case 15).—Roentgenogram in a case of varicose veins of nine years' duration with ulceration. Marked periosteal new bone formation of the shafts of the tibia and the fibula is evident. Arthritic lipping of the astragalus (*A*) is noted in the lateral view.

RESULTS OF STUDIES

In seven cases in which there were active ulcerous lesions overlying the lower part of the leg there was periosteal new bone formation involving either the tibia or the fibula or both. In addition to the periostitis, in three of these seven cases there were arthritic changes in the joints of the foot and ankles (fig. 1).

There were nine cases among the thirty studied in which the necessary roentgenographic evidence was present to establish a diagnosis of chronic arthritis. In each of these there was an associated varicose ulcer, either active or healed and near the ankle joint. In one of these cases the patient had received a fracture of the tibia and fibula eleven years before. Varicosities and an ulcer distal to the site of the fracture developed subsequently. Roentgenograms of the foot revealed marked arthritic changes, most probably from an angulation at the site of the fracture which gave a poor weight-bearing alinement at the ankle joint (fig. 2).

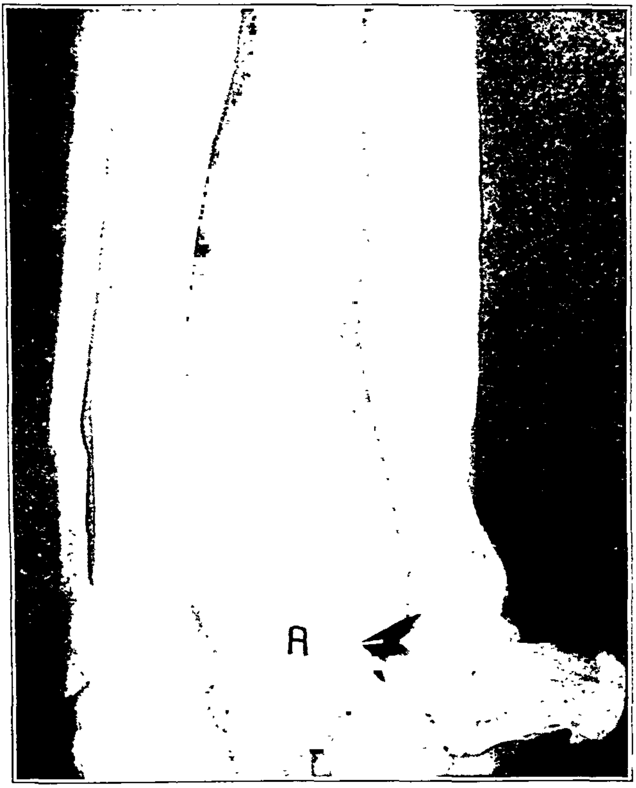

Fig. 2 (case 11).—Roentgenogram in a case of varicose veins of four and one-half years' duration with ulceration. An eleven year old healed fracture with angulation and poor weight-bearing alinement at the ankle joint is evident. The arthritic changes in the tarsal bones (*A*) were probably of "mechanical" origin.

In twenty-one cases there was no roentgenographic evidence of arthritis, even though in nine of these there were varicose ulcers. The results are shown in the accompanying table.

COMMENT

Chronic arthritis of the joints of the ankle or foot could not be demonstrated in twenty-one of the thirty cases of long-standing passive congestion of these parts resulting from varicose veins (fig. 3). In nine cases there was some evidence of arthritic changes, but in each there was either an associated active or a healed ulcer in the region of the ankle point. In none of these cases were there marked changes in the joints except in the one in which there was an added "mechanical factor" from a poor weight-bearing alinement at the ankle joint due to malposition of a fractured tibia.

Data in Thirty Cases of Long-Standing Venous Stasis Due to Varicose Ulcers

Case	Age	Sex	Leg or Legs Involved	Varicose Ulcer	Arthritis of Ankle or Foot Joint	Ossifying Periostitis	Duration, Years
1	65	M	Both	0	0	0	25
2	69	F	Left	Above ankle	Slight	0	5
3	64	F	Both	Large; healed	Slight	0	50
4	46	M	Both	+	0	0	2
5	45	M	Both	0	0	0	6
6	67	F	Both	0	0	0	Years
7	45	F	Both	0	0	0	Years
8	48	M	Both	Left	0	0	5
9	43	M	Both	Right	0	Tibia	2½
10	53	M	Both	Right ankle	+	0	26
11	56	M	Both	Old fracture; ulcer	+	Tibia and fibula	4½
12	83	M	Both	+	+	0	Many
13	46	M	Right	Right	0	0	1
14	29	M	Both	+	0	0	10
15	62	M	Left	+	+	Tibia and fibula	9
16	36	M	Both	+	+	Tibia and fibula	20
17	58	M	Left	+	0	0	4
18	39	M	Left	+	0	Tibia	15
19	59	M	Both	0	0	0	Few years
20	60	M	Both	0	0	0	6
21	48	M	Both	0	0	0	8
22	52	F	Both	Right ankle	+ (right)	0	Years
23	44	M	Both	+	0	Tibia and fibula	12
24	57	F	Right	Healed	+	0	25
25	32	M	Both	Left	0	0	12
26	32	F	Both	0	0	0	6
27	65	M	Both	Left	0	Fibula	Years
28	31	F	Both	0	0	0	2
29	40	F	Both	0	0	0	5
30	35	M	Both	0	0	0	8

In one of the cases of most severe bilateral varicose veins, one of twenty-five years' duration with large ulcerous lesions over the lower third of the leg for several years and diffuse extensive edema of the foot and ankle, eczematous changes of the skin and cyanosis, only minor arthritic changes were observed (fig. 4).

Hence, in cases of marked venous stasis resulting from varicose veins, chronic arthritis did not develop unless there was an added element of ulcerous infection near the ankle joint, and then the changes were not of an advanced degree.

In studies on the circulation of the extremity with varicose veins, de Takáts and his co-workers[1] concluded that there is an increase in venous pressure with a resultant marked edema. In addition, they found that the carbon dioxide content of the blood of the varicose veins of the leg is increased and the oxygen content is decreased. These workers also studied the histamine reaction of persons with varicose veins of the extremities and noted a delayed reaction or absence of reaction, suggesting an impaired arterial circulation to the part. They explained eczema and periosteal thickening as a result of the venous congestion.

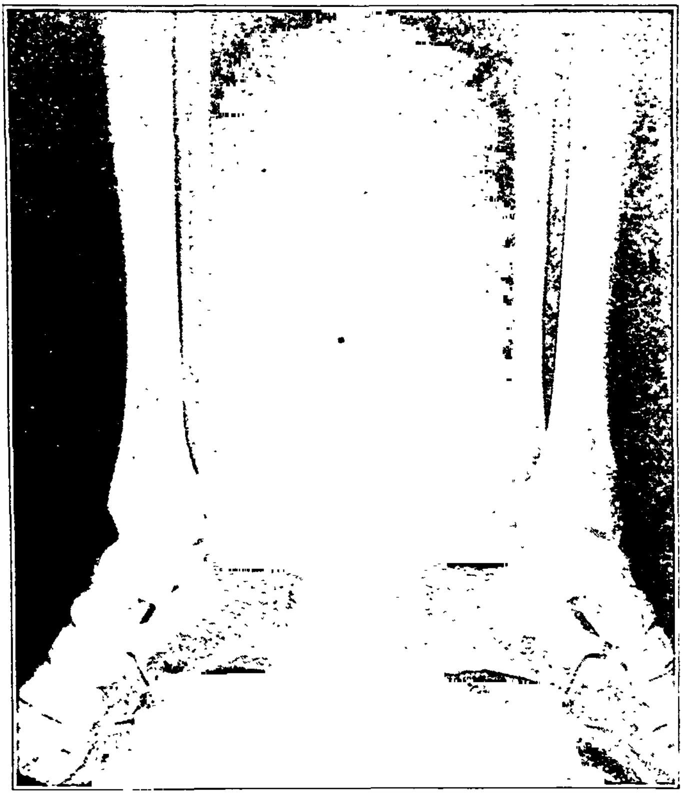

Fig. 3 (case 7).—Roentgenogram showing no definite demonstrable arthritic changes in a case of varicose veins of many years' duration without ulceration.

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[1] de Takáts, G.; Quint, Harold; Tillotson, B. I., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**:671 (Feb.) 1929.

Bernstein[2] made experimental observations on the influence of venous stasis in the production of chronic arthritis by ligating the lumbar vertebral veins of dogs. He examined the lumbar vertebrae after two years and concluded that changes of chronic arthritis had occurred. The clinical observations outlined do not substantiate these experimental findings. In direct contrast to the work of Bernstein[2] are the observations of Goldhaft, Wright and Pemberton,[3] who demonstrated that obstruction of the arterial blood supply to the patella in dogs resulted in chronic arthritis. This work, they stated, verified the original and similar observations of Wollenberg[4] in 1909. Adson and Rowntree[5] assumed that the changes of chronic arthritis in younger persons are due to circulatory changes of a vasospastic type. This opinion was also expressed by Goldhaft, Wright and Pemberton.

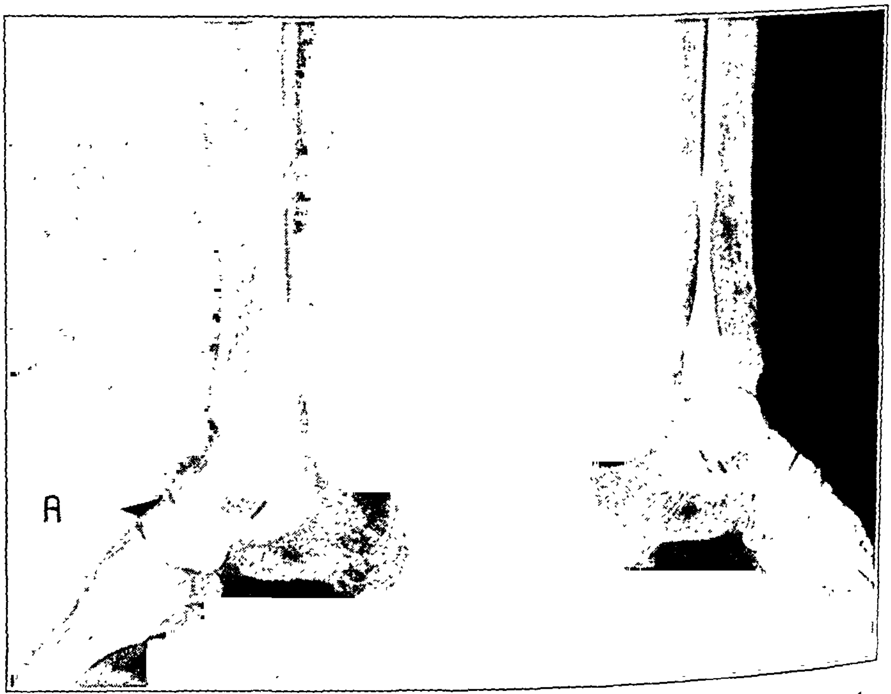

Fig. 4 (case 24).—Roentgenogram showing slight lipping of the tarsal bones (*A*) in a case of varicose veins of twenty-five years' duration with an old healed ulcer.

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[2] Bernstein, M. A.: Experimental Production of Arthritis by Artificially Produced Passive Congestion, J. Bone & Joint Surg. **15**:661, 1933.

[3] Goldhaft, A. D.; Wright, L. M., and Pemberton, R.: The Production of Hypertrophic Arthritis by Interference with the Blood Supply, Am. J. M. Sc. **180**:386, 1930.

[4] Wollenberg, quoted by Goldhaft, Wright and Pemberton.[3]

[5] Adson, A. W., and Rowntree, L. G.: The Surgical Indications for Sympathetic Ganglionectomy and Trunk Resection in the Treatment of Chronic Arthritis, Surg., Gynec. & Obst. **50**:204, 1930.

There is evidence to substantiate the statement that venous stasis hastens the repair of experimentally made bone defects (Pearse and Morton[6] and McMaster and Roome[7]). Harris[8] has shown that venous stasis resulting from various pathologic processes not uncommonly accelerates the growth of long bones in children. In these conditions, however, the venous stasis exerts an influence first on bone and periosteal elements stimulated to repair by trauma and secondly on immature cartilage and bone cell elements which are actively proliferating, and not on mature, relatively inactive cartilage and bone elements, as in these cases of varicose veins.

In discussing arthritis deformans (chronic arthritis), Lang[9] considered functional and mechanical trauma of the first importance. This is often noted clinically and is illustrated in figure 2.

Ossifying periostitis associated with long-standing varicose ulceration is often noted (Morris[10] and Kilbourne[11]). These changes are explainable on the basis of congestion plus infection and are well shown in figure 1. Somewhat similar changes in the bones of the forearm and leg are noted in secondary hypertrophic osteo-arthropathy. These changes, according to Locke[12] are due to two factors, namely, stasis and toxemia. The latter has its origin most often in some long-standing chronic pulmonary lesion. Locke[12] expressed the belief that occasionally in some cases of clubbing of the fingers and toes associated with ossifying periostitis of the long bones in which only a cardiac weakness exists stasis alone may account for the changes. Similar periosteal reactions were noted in the foregoing clinical cases in which stasis plus infection was present, but no periosteal new bone formation could be demonstrated in cases of venous congestion in which there was no associated infection.

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[6] Pearse, H. E., Jr., and Morton, J. J.: The Influence of Alterations in the Circulation of the Repair of Bone, J. Bone & Joint Surg. **13**:68, 1931.

[7] McMaster, P. E., and Roome, N. W.: The Effect of Sympathectomy and of Venous Stasis on Bone Repair, J. Bone & Joint Surg. **16**:365, 1934.

[8] Harris, R. I.: The Effect of Lumbar Sympathectomy on the Growth of Legs Shortened from Anterior Poliomyelitis: A Preliminary Report, J. Bone & Joint Surg. **12**:859, 1930.

[9] Lang, F. J.: Osteo-Arthritis Deformans Contrasted with Osteo-Arthritis Deformans Juvenilis, J. Bone & Joint Surg. **14**:563, 1932.

[10] Morris, D. H.: The Deeper Structural Changes Arising from Varicose Ulceration, Surg., Gynec. & Obst. **30**:72, 1920.

[11] Kilbourne, N. J.: Leg Ulcers of Unrecognized Etiology, J. A. M. A. **98**: 1955 (June 4) 1932.

[12] Locke, E. A.: Secondary Hypertrophic Osteoarthropathy, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, London, Oxford University Press, 1921, vol. 4, pt. 2, p. 431.

SUMMARY

Chronic arthritis of the joints of the ankle or foot could not be demonstrated roentgenographically in twenty-one of thirty cases of long-standing passive congestion and edema of these parts resulting from nonulcerated varicose veins.

In nine of the thirty cases there was roentgenographic evidence of chronic arthritis of the joints of the ankle and foot, but in each there was associated ulceration of the leg or near the ankle joint in addition to the passive congestion from existing varicose veins.

Ossifying periostitis of either the tibia or the fibula or both did not occur from venous stasis alone but did occur in seven cases in which ulcerous lesions existed with the varicose veins.

FIBROBLASTIC TUMOR OF THE EXTREMITIES

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The fibroblastic tumor is among the most common of all the soft tissue tumors involving the extremities and is exceeded in number only by the benign lipoma. The tumor may originate from any area in the connective tissue stroma of the limb and therefore may be found attached to, or growing within, any of its special structures. Fibroblastic tumors range in degree of malignancy from the questionably neoplastic fibrous nodule, which arises as a reparative reaction to local irritation, to the malignant fibrosarcoma. However, such tumors, regardless of form or area of origin, present a clinical and pathologic similarity which justifies their inclusion in a single group. It is partly the object of this paper to demonstrate this fact and to demarcate the group of tumors to which it applies. Before entering into a discussion of their special characteristics, it is necessary that a clear definition of terms be given. A fibroblastic tumor is a neoplasm of mesodermal origin, composed of cells the ultimate function of which is the production of fibrous connective tissue. Such tumors vary within the limits of precursing tissue structure and of adult connective tissue variations. Two factors have tended to obscure the recognition of fibroblastic tumors of the extremities: First, fibroblastic tissue, being a component of almost every tissue of the extremity, may be found in greater or lesser quantity in almost every neoplasm of this region. Second, the earlier the developmental stage of the tissues comprising any of several mesodermal tumors, the more closely do they resemble each other in histologic appearance. It is essential that the variations to which the true fibroblastic tumors are subject be clearly recognized. Knowledge of the path of development (table 1) of the various types of adult connective tissue (table 2) is elementary but fundamental to a proper understanding of this group.

In the components of the fibroblastic tumor no cellular structure is recognized below the mesenchymal, and this only in its later stages, bordering on embryonal connective tissue. The structure of the tumor

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Read before the New York Academy of Medcine, Section of Orthopedic Surgery, Oct. 16, 1936.

From the Hospital for Joint Diseases (Service of Dr. S. Kleinberg) and the Orthopedic Service of Mount Sinai Hospital.

is characterized by the presence of typical stellate cells embedded in a homogeneous fluid matrix. In a more advanced state mucoid substances appear in the matrix, giving certain microchemical stain reactions, which are recognized as specific for myxomatous tissue. At a still later stage the myxomatous tissue disappears, and the adult fibroblastic cell appears, the chief function of which is to produce and/or support "collagen and argyrophile fibers."[1] This adult cell is the typical spindle cell of fibrosarcoma. In the adult stage connective tissue varies normally in the density of its cellular and fibrous structures, in its vascular and adipose tissue content and in the quality and quantity of its wandering tissue cells. These variations are conditioned by the demands of regional structure and function.

Table 1.—*Development of Connective Tissue*

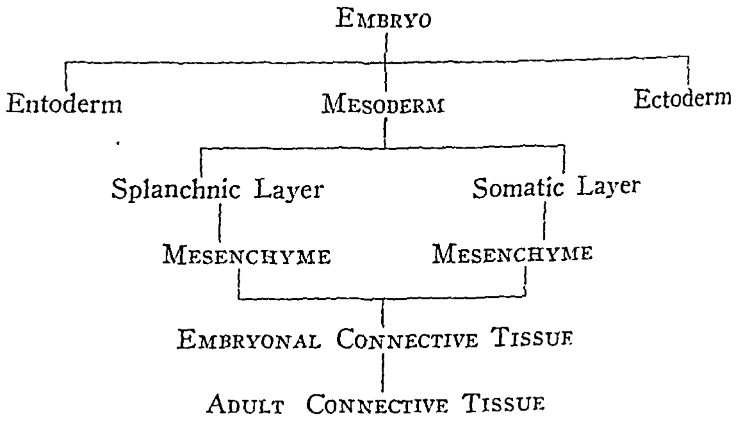

Table 2.—*Variations in Adult Connective Tissue*

Adult Connective Tissue........................	Embryonal * Reticular Fibrillar	Areolar Dense fibrous Elastic

* Embryonal connective tissue is not found normally in the adult but appears during connective tissue repair and neoplasia.

In summary, a fibroblastic tissue tumor is defined and qualified by the fact that its predominant cell possesses the property of forming fibrous tissue. The tumor may present the structure of this tissue in any form from its adult stage to any of its precursing stages. For the benign form of tumor common usage has retained the name *fibroma*, but for the malignant form there has been confusion owing to a superfluity of names. Among these are sarcoma, spindle cell sarcoma, round cell sarcoma, oat cell sarcoma and pleomorphous cell sarcoma, fibroblastic cell sarcoma and fibrosarcoma. The last two terms most suitably define the tumor, and since fibrosarcoma is less cumbersome it is herein adopted, and its general use is urged. The other terms merely describe structural variations in an identical tissue and serve unnecessarily to confuse a specific clinical entity.

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[1] Stout, A. P.: Human Cancer, Philadelphia, Lea & Febiger, 1932.

It must be noted at this point, however, that myxomatous tissue is not only associated with the fibroblastic tumor but may appear alone or as a part of any neoplasm of mesodermal origin. Furthermore, the developmental concept of oncology does not imply that every fibroblastic neoplasm must pass through a myxomatous stage before becoming predominantly fibrous. The nature of the tissue structure of a given tumor depends on the degree of differentiation of its cells at the time of active proliferation. In a number of cases in my collection specimens were taken from recurrent growths. I have never observed a change in the quality of cell structure in a fibroblastic tumor, although I have observed changes in the quantity or density of the cellular content.

RELATIVE FREQUENCY

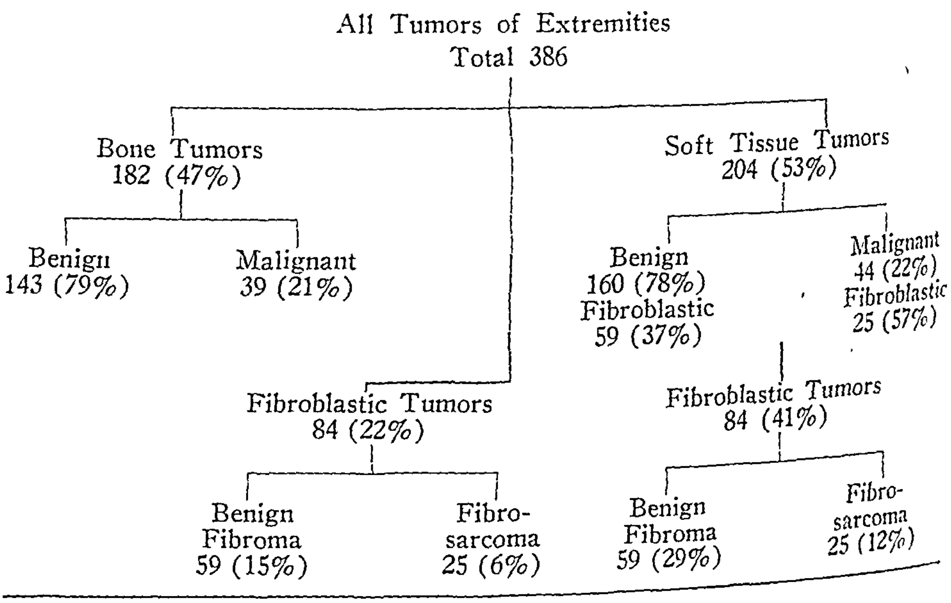
Regrettably, the literature gives no idea of the relative frequency of fibroblastic tumors of the extremities. Valuable reports of fibrosarcoma are usually based on series of from 5 to 19 cases. Papers reporting therapeutic results in large groups (up to 678 cases) do not designate the specific character of the sarcomas examined, and as the complex family of soft tissue sarcoma embraces a wide assortment of tumors, such studies are of little help. Recently I attempted to determine within a reasonable margin of error the actual and the relative frequency of fibroblastic tumors of the extremities. For this purpose the diagnostic files of the Hospital for Joint Diseases from 1930 to 1935 inclusive were consulted. The diagnoses for these files were copied from the pathologists's report in all cases of tumor in which operation or biopsy was done, and clinical diagnoses were used only in the cases of inoperable tumor or in those cases in which for some other reason operation was not performed. The last two groups form a small proportion of the cases of tumor seen at the hospital. No cases are included in which the diagnosis was made in the outpatient department. The relative figures, based on this list, are given in table 3.

In actual frequency, 84 fibroblastic tumors of the extremities were seen in the various services of the Hospital for Joint Diseases from 1930 to 1936. This represented 22 per cent of all tumors of the extremities seen within that period and 41 per cent of the soft tissue tumors of the extremities.

SURGICAL PATHOLOGY

Since the diagnosis of any tumor depends on the interpretation of histologic material, it is incumbent on the surgeon who deals with a growth to have a reasonable knowledge of its pathologic structure. The morphologic picture of a typical fibroblastic tumor is characteristic. There is a proliferation of cells in a connective tissue stroma, with a coincident increase in fibers. Where the neoplasia of spindle-shaped fibroblasts is visibly evident, the commonly used hematoxylin-eosin stain may suffice for diagnosis. However, in those fibroblastic tumors in which the cells are immature or in which the histologic field does not conform to that of the typical specimen, purely cytologic study may be insufficient. One or more of several special tissue stains will then demonstrate the presence of excessive fiber formation and the relationship between fiber and cell content or between the predominant neoplastic cell and its host tissue. The Van Gieson and the Mallory stain for connective tissue and the Laidlaw stain for silver-negative fibroblastic cells are among the more common of these differential stains. The first two stains are well known.[2] They serve to disclose the presence of fibers within the stained field and are most useful in defining fibroblastic tumors of the adult cell type. The Laidlaw silver

TABLE 3.—*Relative Frequency of Fibroblastic Tumors of the Extremities (1930-1936)*



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[2] Laidlaw, G. F.: Silver Staining of the Skin and of Its Tumors, Am. J. Path. 5:239, 1929; in Stout.[1]

stain finds its most valuable application among fibroblastic tumors when the cells are of the immature type, that is, when the cells are not characteristically spindle shaped.

A difficult complication in the study of the fibroblastic tumor is the fact that the growth may arise from within or invade other special tissues, such as fat, bone, muscle, nerve sheaths or the walls of blood vessels. Whether or not a given tumor containing adipose and fibrous tissue or muscle fibers and connective tissue is a fibroblastic tumor may sometimes be a matter of judgment rather than a matter of fact. Judgment in these cases can be confirmed only by the subsequent history of the tumor. Fortunately, these instances are relatively rare, and more extensive use of differential stain technic will decrease their number still further. The presence of an abundant vascular tissue in a connective tissue neoplasm requires special consideration. Such tumors have been classified as angiosarcoma. Livingstone and Klemperer in 1926 discussed this type of tumor under the term malignant angioma.[3] They pointed out that the name was misleading and that the neoplasm showed merely the "simultaneous presence of undifferentiated mesenchymal and angiomatous structures in a malignant tumor." Stout agreed that the term angiosarcoma should be dispensed with, since the tumor in question is either a malignant angioma in a fibroblastic matrix or a highly vascular fibrosarcoma. From the reported cases and from the cases presented here, there is no evidence that the vascularity of a fibroblastic tumor influences its degree of malignancy. A benign fibroma may present a relatively extensive vascular invasion, as in 1 of my cases in which the tumor had remained static for about fifteen years before an acceleration of growth invited surgical removal. On the other hand, I have listed in my series of cases 1 in which a vascular fibroblastic tumor of the deltoid region was excised in 1932 and recurred within a year. In reviewing the material there is no morphologic indication which even in retrospect would associate the grade of malignancy with the extent of vascularity. These tumors acted clinically in a manner characteristic of fibroblastic tumors.

One of the most confusing diagnoses in the field of oncology has been that of neurofibrosarcoma, or neurogenic sarcoma. The work of Masson[4] and the recent studies of Stout[5] and Foot[6] have helped greatly to clarify this obscure problem. There can be differentiated from the general group of tumors of the peripheral nerves a true fibroblastic sarcoma arising from the connective tissues of the nerve sheaths. Because of its association with neurogenic tissues, histologic sections may include areas showing nerve fibers, or schwannian elements, but the predominant neoplasia is seen to be among fibroblastic cells. A fibroblastic tumor derived from this source often is associated with the generalized neurofibromatosis of Recklinghausen. It is more likely to be encapsulated than are similar tumors derived from other sources. I have indicated in a previous publication that a fibroblastic tumor of nerve sheath origin frequently remains static over a long period before showing a renewed acceleration of growth.[7] However, this observation is in all probability related to the tendency toward the formation of a capsule. Late increase in the rate of growth may occur in any fibroblastic tumor, even in the absence of a demonstrable capsule.

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[3] Livingston, S. F., and Klemperer, P.: Malignant Angiomas, Arch. Path. **1**:899 (June) 1926.

[4] Masson, P.: Experimental and Spontaneous Schwannomas (Peripheral Gliomas), Am. J. Path. **8**:367 and 389, 1932.

[5] Stout, A. P.: Malignant Tumors of the Peripheral Nerves, Am. J. Cancer **25**:1, 1935.

[6] Foot, N. C.: Peripheral Neurogenic Tumor, Am. J. Clin. Path. **6**:1, 1936.

A fibrosarcoma arising from the outer layer of periosteum may either grow away from the bone or invade its substance. In the former case, that of the so-called parosteal or periosteal fibrosarcoma, the bone may be surrounded by tumor tissue, with possibly some superficial erosion of the cortex. If the tumor invades the bone it is usually diagnosed both by roentgenographic and by clinical examination as a bone tumor. I have several such cases in which the iliac bones are involved. However, histologic study in these cases shows a pure fibroblastic tumor with no signs of bone formation. Geschickter has reported a series of cases in which fibrosarcoma invading bone substance arose not only from the outer layer of the periosteum but from adjacent soft tissues.[8] In so-called fibroliposarcoma or the benign form, fibrolipoma, a similar approach will simplify the problem. If excessive fibrillar proliferation is present in an adipose field, the diagnosis of fibroma or fibrosarcoma is warranted. If there is an obvious proliferation of fatty tissue and only a normal amount of fibrous tissue is present in the stroma, the growth is a lipoma or a liposarcoma. It should not be forgotten in this connection that the fibrous content of adipose tissue varies in different regions of the body. Only in those specimens in which there is simultaneous neoplasia of fatty tissue and fibroblastic tissue can the use of the term fibrolipoma or fibroliposarcoma be justified. The developmental or embryologic relationship between these two mesodermal derivatives is common knowledge. However, at the stage of tumor formation their differentiation has become too far advanced for metaplasia.

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7. Bick, E. M.: Fibrosarcoma of the Extremities, Ann. Surg. **101**:759, 1935.

8. Geschickter, G. F.: So-Called Fibrosarcoma of Bone: Bone Involvement by Sarcoma of Neighboring Soft Parts, Arch. Surg. **24**:231 (Feb.) 1932.

The significance of myxomatous tissue in a fibroblastic tumor was discussed previously. The presence of mucoid substance as demonstrated by the mucicarmine stain determines its diagnosis and differentiates it from the more common and often mistaken edema of simple fibrous tissue. Thibaudeau and Kress[9] have published one of the most complete studies of myxomatous tumors in recent years. Their report is based on a study of 51 tumors which these authors grouped as follows: 9 as myxofibroma, 39 as myxosarcoma and 3 as myxoliposarcoma. Approached from my point of view, 48 of the 51 were fibroblastic tumors and 39 were malignant. The authors stated:

> An attempt was made to correlate the histological appearance of the growth with the clinical course of the disease, but we were unable to determine that any histological feature observed in our sections could aid us in determining the degree of clinical malignancy. We did observe, however, that those tumors in which mitosis was most marked were as a rule most rapidly fatal.

In my own collection of tumors I have thus far 6 fibroblastic tumors of the extremities exhibiting areas of myxomatous tissue. The ages of the patients varied from 24 to 60; 4 of the 6 tumors occurred on the thigh. This is entirely in accord with the larger series of cases reported by Thibaudeau and Kress. I am in entire agreement with their views on the inadequacy of histologic interpretation of the degree of malignancy; furthermore, I do not believe that the presence of myxomatous tissue in any way influences the prognosis of the tumor as compared with fibroblastic tumor which does not contain demonstrable myxomatous tissue.

The presence of muscle fibers in a tumor of the extremities demands clear oncologic differentiation. One must first distinguish between tumors composed of true myoblastic elements, such as myoblastoma or rhabdomyoma, and those derived from associated tissues which in the course of neoplasia have infiltrated the fascicles of the muscles.[10] That the fibrosarcoma is the most common of all tumors of skeletal muscle was shown by me in 1934.[11] Of 35 unselected tumors involving skeletal muscle reports of which were collected at that time, 50 per cent were fibroblastic. The extensive distribution of connective tissue surrounding and within muscle substance offers a wide surface area for the inception of fibroblastic neoplasia. The clinical data collected concerning fibroblastic tumors of skeletal muscle differed in no way from those concerning fibroblastic tumors of other tissue origin in the extremity, and here, too, the presence of an associated tissue did not change the general rate of growth, recurrence or metastasis.

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[9] Thibaudeau, A. A., and Kress, L. C.: Myxosarcomata, Am. J. Cancer **23**:267, 1935.

[10] Klemperer, P.: Myoblastoma of the Striated Muscle, Am. J. Cancer **20**: 324, 1934.

[11] Bick, E. M.: Skeletal Muscle Sarcoma, Ann. Surg. **99**:949, 1934.

CLINICAL OBSERVATIONS

In considering fibroblastic tumors of the extremities as a specific group, certain repeated observations become emphatic. For the most part, their natural history runs to a true form with few modifying exceptions. Encapsulation is found more frequently in fibrosarcomas derived from nerve sheaths and probably related to this is the tendency of this type of tumor to remain static for long periods of time before showing progressive growth. As a group, even without these exceptions, fibroblastic tumors vary greatly in malignancy. The diagnosis of benign fibroma is not a factual statment; it is an interpretation of histologic appearance and must be so regarded. A fibroma is benign only when after years of follow-up study there has been no recurrence. A true fibroma, no matter how casual its clinical or histologic appearance, must be considered a potential fibrosarcoma until its benignity is established by its subsequent behavior. Except for the general proposition that cellular tissues are more likely to be rapidly malignant than are relatively acellular tissues, I have not been able to establish any correlation between the histologic structure of a fibroblastic tumor and its relative malignancy.

The average period of time between the first recognition of tumor and death in the fatal cases was between two and three years, and all but a few of the patients died within that period. In 14 cases of fibrosarcoma in which the condition has not yet proved fatal and in which excision or excision plus irradiation was the treatment employed, recurrence was found to take place as follows:

Case No.	No. of Recurrences	Time After Operation, Yr.
1	2	2.0
2	1	1.0
3	1	0.5
4	1	1.0
5	1	0.8
6	1	0.5
7	2	2.0
8	4	3.0
9	2	2.0
10	2	2.0
11	1	4.0
12	1	1.0
13	3	4.0
14	1	2.0

These figures cannot be converted into statistically significant averages. However, in general, they indicate that the expectancy of recurrence is highest in the first postoperative year and precipitately decreases after that. In other words, if a fibroblastic tumor will recur, it will most likely do so within the first year; the probability of benignity is very high after that period if recurrence has not taken place. The clinical application of this is important. After the removal of an apparently benign fibroma, a follow-up period of one year is reasonably sufficient if no recurrence has taken place. However, when a recurrent growth has been excised, secondary recurrence appears, if at all, in less time than did the first. The acceleration of recurrence increases with each excision. In my series of cases the addition of irradiation to the treatment of a recurrent growth has not seemed to influence this fact. I can find no evidence in my cases to maintain the often-repeated hypothesis that all recurrent tumors are more cellular than are the primary specimens. Some are, and some are not. The rapidity of clinical recurrence is the only important criterion of the grade of malignancy of any given neoplasm.

Clinical observations on fibroblastic tumors of the extremities present a fairly uniform picture, regardless of their associated tissues or structures. I have found no significant sex distribution. In one of my series,[7] 25 cases occurred in males and 17 in females; in another somewhat overlapping series the sex distribution in 46 cases was exactly equal. It must be noted here, however, that a recent author reporting a similar series found the proportion to be in the neighborhood of 2:1, favoring males.[12] By considering the cases in both series, one might assume that fibroblastic tumors of the extremities are somewhat more common in males. Fibroma of the extremities occurs with almost equal frequency in each age group up to 50 years. The malignant form may appear at any age but is most common during the fourth and fifth decades. Sixty-four per cent of the fibromas in my series occurred in the upper extremity and 36 per cent in the lower. In both instances, about 80 per cent were found in the distal portions of the limbs, that is, on the hands and fingers or on the feet and toes. In these areas the most frequent host tissue was the tendon sheath. However, fibroblastic tumors involving the tendon sheaths of the distal segments of the limb represented only a small proportion of the malignant growths. Statistically, there appears to be some inexplicable predilection of certain parts of the limb for the malignant form of fibroblastic tumor. About 50 per cent of my series of fibrosarcomas of the extremities occurred in the thigh, and almost all of these involved the lower two-thirds. Of fibrosarcomas found on the upper extremity, about one half involved the forearm. Whether the relatively high

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[12] Meyerding, H. W.; Broders, A. C., and Hargrave, R. L.: Clinical Aspects of Fibrosarcoma of the Soft Tissues of the Extremities, Surg., Gynec. & Obst. **62**:1010, 1936.

degree of musculofascial stress and strain centered in these regions is significant or not is conjectural. However, the common distribution of fibrosarcoma at these segments is a valuable differential suggestion and distinguishes the growth from the more common benign lipoma, which occurs so predominantly about the shoulder and in the gluteal regions.[13] Pain is rarely of diagnostic or prognostic significance. It is almost never severe; considerable tumefaction may be present with relatively moderate discomfort. Radiation of pain along a nerve suggests only proximity or anatomic involvement of that nerve and is of no special importance. A fibroblastic tumor has a characteristic firmness on palpation. It is not as "stony hard" as most carcinomatous nodules or as soft as most lipomas. Mobility of the tumor depends on the tissue of origin. Fibromas vary in size from that of a pea to that of an egg. However, the smallness of a fibroblastic tumor is no indication of its innocence, since I have repeatedly seen a small nodule which was treated as a benign fibroma recur with a considerable degree of malignancy. A primary fibroblastic tumor of the extremity larger than an average-sized walnut has almost invariably proved to be a fibrosarcoma.

The tendency of fibrosarcoma is to grow by expansion rather than by infiltration. Ewing pointed out the propensity of this growth for following the paths of nearby blood vessels.[14] This leads to early invasion of the vascular system and hence in metastasis to direct involvement of the lungs and abdominal viscera. In fibrosarcoma of the extremities the regional lymph nodes are never involved, unless by direct extension from neighboring structures. Conversely, regional involvement of the lymph nodes is presumptive evidence against this neoplasm.[7] In my cases metastasis has occurred between two and four years after the original appearance of the tumor. However, the time of metastasis is unquestionably influenced by the treatment employed.

TREATMENT

The treatment of fibroblastic tumor of the extremities must be discussed with the greatest restraint. Reports in the literature vary considerably, and in most instances they consider a multiplicity of therapeutic measures, which confuses the results. For example, the method of multiple excisions with irradiation and final amputation is difficult to evaluate. The possibility of local excision acting as a stimulant to neoplasia, together with variations in the technic of irradiation used in the past twenty years, casts doubt on the virulence of a primary malignant growth. Of even greater importance is the change in diagnostic concept concerning such tumors. Up to the period from 1925 to 1930, the term sarcoma as applied to soft tissue tumors was almost generic for all malignant tumors other than carcinoma. During this period, under the influence of Ewing,[14] Quick and Cutler[15] and Lewis and Hart,[16] many reports included rather benign neurogenic tumors under the category of sarcoma of the nerve sheath. In the absence of definite diagnostic criteria an evaluation of end-results is futile. A number of reports will demonstrate the variations encountered. Wollner[17] (1926) reported cures in 12.8 per cent of 39 cases of tumor in the advanced stage after surgical treatment and irradiation and in 28.5 per cent of 21 cases in the early stage after surgical treatment alone; De Waard[18] (1927) reported cures in 14 per cent of 74 cases after surgical treatment, and Rostock[19] (1928, in 6 per cent of 35 cases of inoperable tumor after irradiation alone, in 10.5 per cent of 38 cases of "borderline" tumors after incomplete surgical removal and postoperative irradiation and in 37 per cent of 46 cases of operable tumor after excision and irradiation. Hintze[20] (1930), in a report on 678 cases studied five years or longer, stated that cures were obtained in 28.7 per cent of 216 cases by surgical methods, in 39 per cent of 79 cases of recurrent tumors by irradiation, in 39 per cent of 82 cases by surgical methods and irradiation and in 24.9 per cent of 201 cases of inoperable tumor by irradiation. However, this series, even though grouped under the title of sarcoma, included growths which obviously would not today be so classified. Meves[21] (1931) reported cures in 11 per cent of 173 cases and also included cases in which the results were doubtful. The wide variation in percentage of cures, the tendency to broad use of the term sarcoma and the antiquity of many of the case records make judgment extremely difficult. Of more interest is a group of recent reports in the American literature. Pelletier[22] has been reporting small series of cases of fibroblastic tumor from the Pondville Hospital in which a careful follow-up study was made. The results have not been encouraging. In several cases in which it has been five years since treatment, recurrences appeared later in spite of adequate roentgen therapy. French[23] (1932) published a valuable series of end-results in 16 cases of fibrosarcoma, in 8 of which the growth involved the extremities. One patient with a fibrosarcoma of the thigh was well six years after amputation of the tumor, which had been present six months. One patient was well two years after amputation. The other patients, on whom amputation had not been performed, either died or had a recurrence. (One case was too recent for the results to be evaluated.) Leucutia[24] (1935) reported survivals of from five to twelve years in 34 per cent of 101 cases of sarcoma of the soft parts in which high voltage roentgen therapy and surgical measures were employed. However, he defined fibroblastic sarcoma as "all those sarcomatous tumors of soft-parts which cannot be placed in any of the well-characterized subgroups." I cannot consider that definition tenable, since it permits too great a latitude in diagnosis. Meyerding, Broders and Hargrave[12] (1936) reported end-results on 132 patients treated at the Mayo Clinic for fibrosarcoma of the extremities. Their figures are as follows: Twenty-one per cent lived for three years after excision or amputation; 17.5 per cent, from five to twenty years; 14.4 per cent, from five to ten years, and 6 per cent, from ten to twenty years.

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[13] Bick, E. M.: Lipoma of the Extremities, Ann. Surg. **104**:139, 1936.

[14] Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

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[15] Quick, D., and Cutler, M.: Neurogenic Sarcoma, Ann. Surg. **86**:810, 1927.

[16] Lewis, D., and Hart, D.: Tumors of Peripheral Nerves, Ann. Surg. **92**: 961, 1930.

[17] Wollner, W.: Ergebnis einer 10 jährigen Sarkombehandlung, Beitr. z. klin. Chir. **138**:39, 1926.

[18] de Waard, T.: Ueber Sarkome und die Resultate der chirurgischen Behandlung, Nederl. tijdschr. v. geneesk. **1**:822, 1927.

[19] Rostock, P.: Indikationsstellung und Dauererfolg der Röntgenbestrahlung bei Sarkomen, Fortschr. d. Therap. **4**:241 (April 25) 1928.

[20] Hintze, A.: Die Erfolge der operativen und der Bestrahlungsbehandlung beim Sarkom, Arch. f. klin. Chir. **162**:345, 1930.

[21] Meves, F.: Der Erfolg der Sarkomtherapie in der Kieler chirurgischen Klinik (1914-1928), Deutsche Ztschr. f. Chir. **231**:691, 1931.

[22] Pelletier, V. A.: Sarcomas, Am. J. Cancer **15**:2418, 1931; (supp.) **21**: 658, 1934.

The great variation in the percentages of reported cures is obvious at a glance and indicates the need for further investigation. From my own series there are not as yet sufficient follow-up data on properly controlled cases to offer a final therapeutic point of view. It has been necessary first to restudy the groups of tumors and to establish clinical and pathologic criteria for control study. However, during the course of this work certain therapeutic observations have become increasingly conspicuous. In general, they tend to agree with the observations in reports such as those of French and Pelletier, in which the results of a careful follow-up study over a period of time in individual cases and a study of adequate histologic material are presented. Of 9 patients with proved fibrosarcoma of the extremities, only 2 are living after five years. In 1 the tumor involved the connective tissue of the knee joint, and an amputation was performed at the time of the first recurrence. In the other, the tumor involved the region of the shoulder and was treated by excision and high voltage roentgen therapy, with no recurrence. A third patient with a tumor involving the thigh is alive four years after excision plus high voltage roentgen therapy; a fourth is alive three years after simple excision. All other patients, 5 in number, died of metastases after two or more recurrent tumors were excised or after a second or third recurrent tumor was amputated. These figures, combined with those of other authors reporting individual cases, suggest the following therapeutic indications. Since the malignancy of a primary fibroblastic tumor cannot as yet be judged by histologic study and since few, if any, such tumors metastasize before at least one recurrence, adequate excision, with or without high voltage roentgen irradiation, is the treatment of choice. The experience of several authors, including myself, has shown cures five years after this procedure. However, recurrence must be an indication for amputation. I have no case as yet, and few have been reported, in which five year cures are recorded after repeated excisions of recurrences. Whether present experiments with changes in the technic of irradiation will alter this rule in the future remains to be seen, but until well controlled end-results are shown irradiation for fibroblastic tumors cannot be depended on.

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[23] French, R. W.: End-Results in a Series of Sixteen Cases of Fibrosarcoma, New England J. Med. **206:**393 (Feb. 25) 1932.

[24] Leucutia, T.: Radiotherapy of Sarcoma of the Soft Parts, Radiology 25: 403, 1935.

Dr. Paul Klemperer, of the Department of Pathology of Mount Sinai Hospital, and Dr. H. L. Jaffe, pathologist to the Hospital for Joint Diseases, rendered invaluable assistance in the study of this material.

EXPERIMENTAL GIANT CELL TUMOR AND CARTILAGINOUS EXOSTOSIS OF BONE

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OMAHA

Incidental to the course of an investigation of an entirely unrelated problem there developed in several rabbits lesions of bone with all the characteristics of cartilaginous exostosis and in two rabbits tumors apparently identical to the giant cell tumor of man. These observations are reported because it is believed that they contribute some information relative to the etiology of these tumors.

The studies were made on fourteen immature rabbits from 1 to 3 months of age. In each a segment measuring approximately 20 mm. was removed from the shaft of the radius on both sides in block resections. In each animal the gap on the right side was bridged with an autogenous transplant of costal cartilage equal in length to the segment of bone removed, and on the left side it was left empty to fill with blood. The results of the original problem, which had for its purpose a comparative study of the repair of the radial defects with and without transplanted cartilage, will be published later.

Since no dressings were applied to the legs and the animals were compelled to bear weight immediately without support, and since the animals were immature, roentgenograms made on the day after operation revealed certain unanticipated complications and findings.

CARTILAGINOUS EXOSTOSIS

It was found that in twelve of the twenty-eight legs that were operated on partial or complete separation and displacement of the distal epiphysis of the ulna had taken place, presumably as the result of one or all of three factors: the prying against the shaft of the ulna at the time of operation, the bending stress of muscular pull and the torsion of weight bearing. Roentgenograms made two, four, eight and twelve weeks later demonstrated, strangely enough, either complete (in seven ulnas) or nearly complete (in five ulnas) spontaneous replacement of the epiphyses. In five of those which were completely reduced, longitudinal growth of each ulna was resumed and progressed normally, and no abnormalities developed. In the remaining seven there were definite disturbances of growth, including both deviation to the side

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Read before the Section on Orthopedic Surgery at the Eighty-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 6, 19 from the normal long axis and retardation of growth in length. Also there developed on the external surfaces of these seven ulnas projecting tumors which grossly and histologically were similar if not identical to the osteochondroma or cartilaginous exostosis observed in man. Two of the tumors were composed entirely of bone and apparently were simple osteomas. The other five were made up of bone which was continuous with the shaft. The outer convex surface of each tumor was covered with a layer of dense connective tissue, beneath which there was a layer of hyaline cartilage, which varied in thickness in different areas, as illustrated in figure 5 *A*. In the deeper layers of this cartilage the cells were arranged irregularly in rows, as in the epiphysial cartilage. In this zone, as shown in figure 5 *B*, the cartilage was undergoing calcification and was continuous with the deeper core of laminated spicules of bone which made up the bulk of the tumor. In the superficial layers of bone there were several small islands of cartilage. The marrow between the bony trabeculae was sparsely cellular and mainly fatty. At the base of the tumor, on its proximal surface, the dense bone of the cortex extended up onto the tumor, having in this area no cap of cartilage.

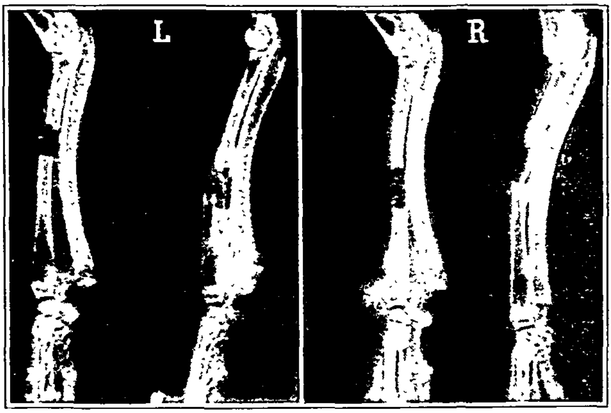

Fig. 1.—Serial roentgenograms of rabbit 9. On the left side of each pair of roentgenograms is shown complete separation of the distal epiphysis of each ulna immediately after resection of a segment of the shaft of each radius. There was complete and spontaneous reduction of these fracture dislocations, as shown in the roentgenograms on the right taken four weeks later. The right ulna resumed normal growth, and a cartilaginous exostosis developed in the left.

As one studies the serial roentgenograms of some of these animals it is possible to build the progressive steps in the evolution of these tumors. Roentgenograms of rabbit 9 (fig. 1) made the day after operation showed complete separation and displacement of both ulnar epiphyses, and those made four weeks later showed spontaneous replacement with no disturbance in the right leg but with the formation of a cartilaginous exostosis and a disturbance of growth in the left ulna. In this instance the tumor appeared to be continuous with the epiphysial cartilage at its distal margin.

In rabbit 4 (fig. 2) there was partial slipping of both ulnar epiphyses, which twelve weeks later resulted in retardation of longitudinal growth but no other abnormality.

In rabbit 8 (fig. 3) both ulnar epiphyses became completely separated and displaced and subsequently became partially replaced. There developed as a result fusion of the epiphysis with the diaphysis and complete arrest of longitudinal growth in the distal ends of both ulnas. In the left one (fig. 3 *A*) there formed a lobulated cartilaginous exostosis, and in the right one, a giant cell tumor, which will be discussed later.

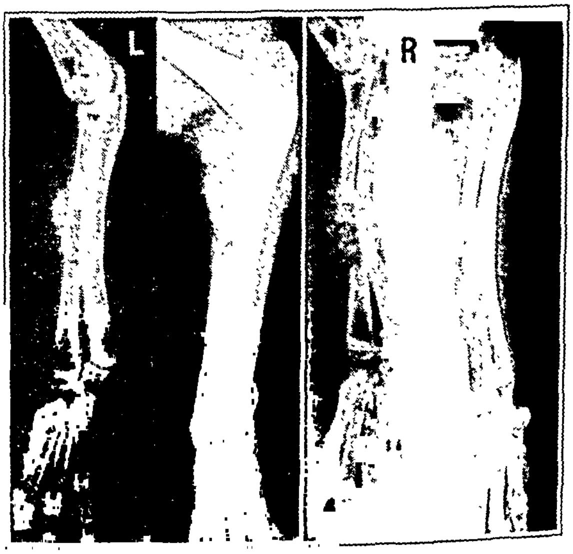

Fig. 2.—Roentgenograms showing slipping with only partial displacement of both distal ulnar epiphyses with subsequent spontaneous reduction and retarded longitudinal growth. No exostosis developed.

In rabbit 3 (fig. 4) the steps in the formation of the cartilaginous exostosis were more clearly demonstrated. Both ulnar epiphyses slipped and subsequently became only partially replaced. The displaced lateral portion of the diaphysis, which normally approximated the epiphysis, was left free to project as a spur as the epiphysis moved distally away from it with continued longitudinal growth.

The histologic structure of these tumors is shown in figure 5.

From these observations, I have made the following deductions. The cartilage which formed a cap over the surface of each tumor was derived from, or was a portion of, the epiphysial cartilage. As separation of the epiphysis occurred, a portion or layer of the cartilage that remained adherent to the projecting edge of the distal end of the diaphysis. It became isolated from the rest of the cartilage, which moved distally away from it in the course of normal longitudinal growth. This isolated cartilage proliferated and continued to lay down bone, which explains the obvious rapid increase in size. As further evidence that the cartilage was derived from the epiphysial disk is the histologic similarity (the row formation of cells) and the appearance in one specimen of continuity between them, suggesting that the displaced segment of epiphysial cartilage had not become completely detached and isolated.

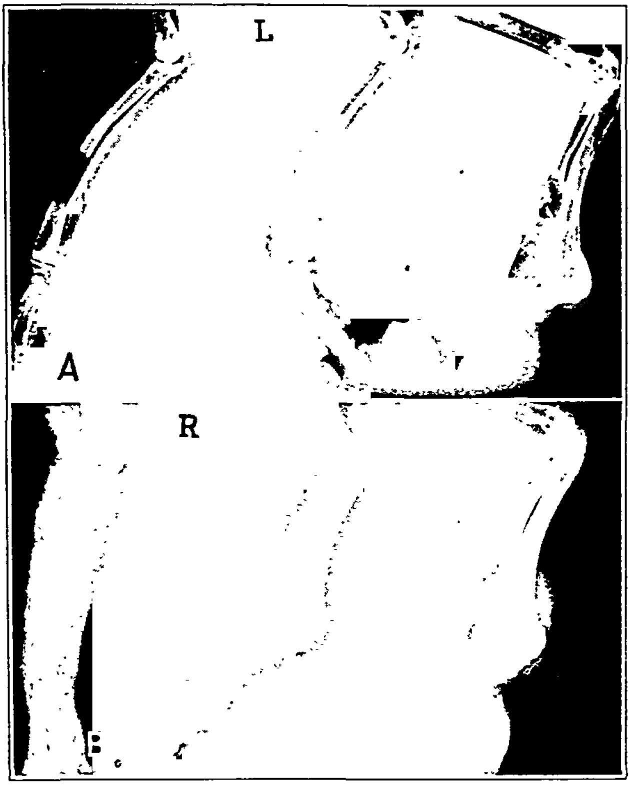

Fig. 3.—*A*, roentgenograms of the left forearm of a rabbit taken immediately after operation and four and twelve weeks later. Note that as a result of epiphysial separation a lobulated cartilaginous exostosis developed in the distal end of the shaft of the ulna. *B*, roentgenograms of the right forearm of the same animal. Note the area of rarefaction in the bulbous distal end of the shaft of the right ulna in the film taken twelve weeks after operation. This contained a giant cell tumor.

COMMENT ON CARTILAGINOUS EXOSTOSIS

As a result of traumatic epiphysial separation and displacement, there developed in a series of rabbits tumors at the distal diaphysial ends of the ulnas. These tumors had the gross and the histologic appearance of cartilaginous exostoses in man; so it is suggested that some of these tumors in man (particularly the solitary ones) may have a similar etiology. In clinical cases an antecedent history of trauma is not infrequently obtained. It is possible that a segment of epiphysial cartilage from the border of the ulna may be displaced embryologically or by trauma with or without some minor epiphysial displacement and subsequently proliferate and lay down bone, giving rise to a tumor.

All investigators of this problem have conceded the possibility of trauma in the etiology of some of the solitary lesions, but it seems unlikely or impossible to explain the multiple and familial types of the disease on this basis alone.

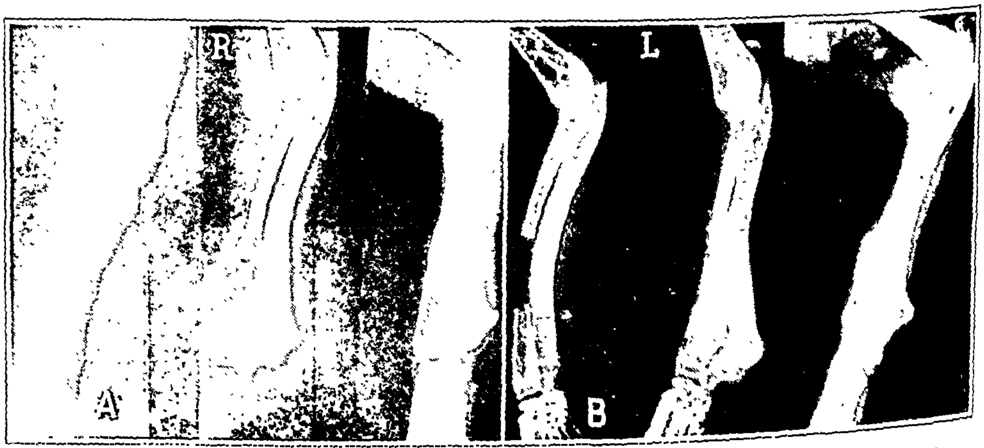

Fig. 4.—*A*, roentgenograms of the right forearm taken immediately after operation and four weeks and twelve weeks later. Note the slipping of the ulnar epiphysis, incomplete reduction, enlargement of the projecting spur of the distal end of the shaft and the distal movement of the epiphysis away from it as growth continued. Also observe the characteristic roentgenographic finding of a giant cell tumor in the distal end of the shaft of the radius in the roentgenogram at the right (twelve weeks after operation). *B*, roentgenograms of the left forearm of the same animal. Similarly persistent partial displacement of the ulnar epiphysis resulted in the formation of cartilaginous exostosis.

Geschickter and Copeland[1] considered cartilaginous exostosis to be

> . . . an exaggeration of a normal bony protuberance intended for the anchoring of an important tendon. At such a junction, nature provides normally for a protuberance of bone bulging through a gap in the periosteum to meet an adjoining tendon, which coöperates in the formation of the attachment by cartilaginous

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[1] Geschickter, C. F., and Copeland, M. M.: Tumors of the Bone, New York, American Journal of Cancer, 1931.

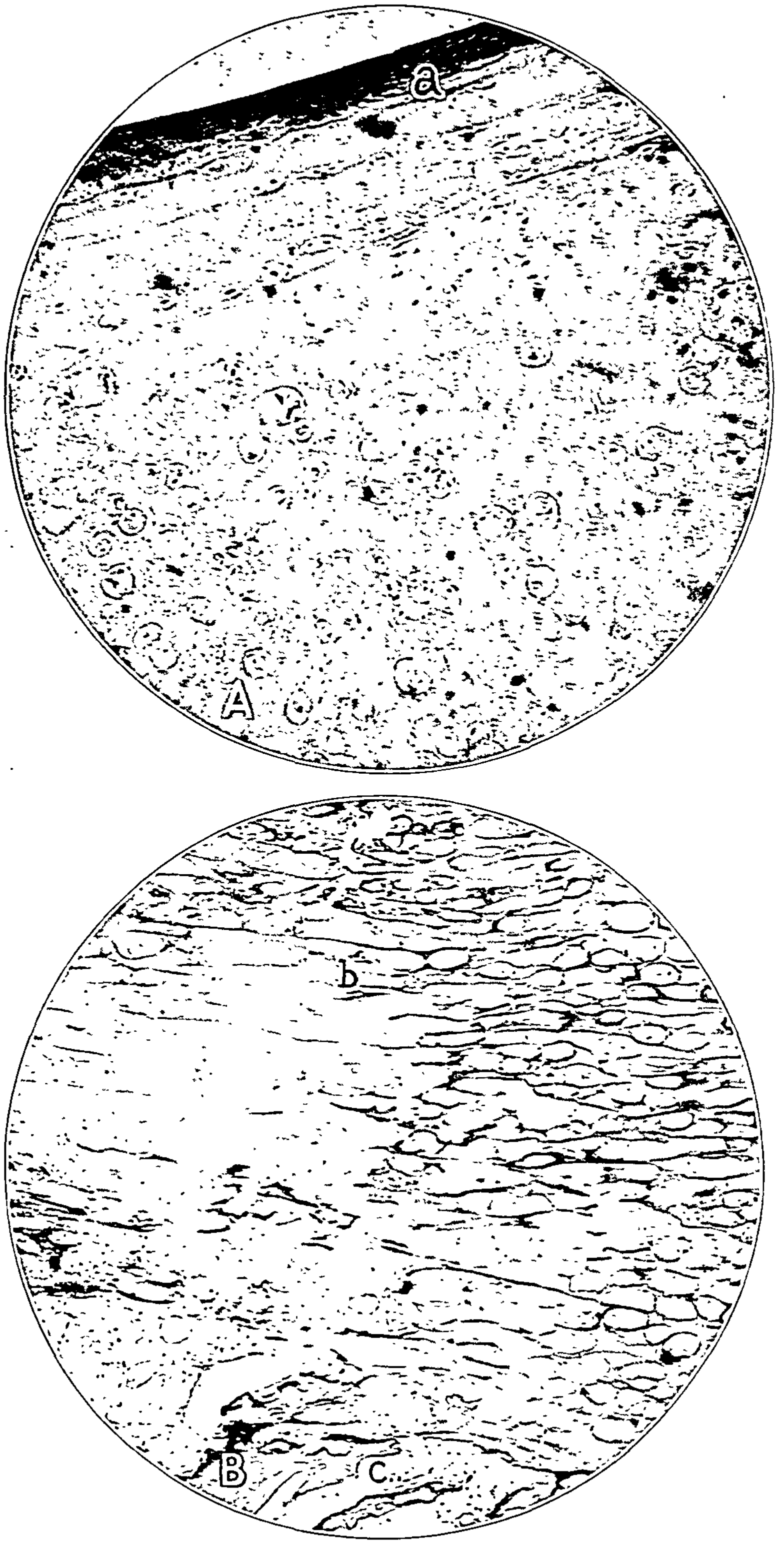

Fig. 5.—High power photomicrographs of cartilaginous exostosis shown in figure 4 *A*. Note the external layer of fibrous tissue covering a layer of cartilage (*a*), the deeper layers of transitional tissue (*b*) varying from calcified cartilage to trabeculae of bone (*c*).

ossification within the substance of the tendon. An exostosis represents a failure in the accurate approximation of the tissue entering into such a junction, the cartilaginous center in the tendon persisting in the form of primitive connective tissue, proliferating in excess, and the protuberance of normal bone beneath extending to form a pedicle or base.

They pointed out:

> In both normal tendons, which attach directly to bone and in normal joints at the reflexion of the joint capsule, proliferating zones apparently acting as normal growth centers may be found. In these proliferating centers early cartilage cells derived from young fibroblasts may be seen, and occasional areas of ossification, a transition of tissues typical of osteochondromas.

They expressed the belief that single cartilaginous exostosis may result from traumatism, the injury either repressing the periosteum and preventing it from covering the bone as it would normally or stimulating the growth of cartilage from the precartilaginous tissue in the growth zone in the end of the tendon. They also stated that "osteochondromas are not related histogenetically to the bone proper nor to the epiphyseal line as so often stated," because these tissues are too highly differentiated.

It would seem impossible to apply this theory of Geschickter and Copeland to explain the origin of the tumors which developed in these rabbits. The relationship to epiphysial displacement is too obvious. Again, these experimental findings offer only presumptive evidence as to the origin of this type of tumor in man.

GIANT CELL TUMOR

In the distal fragment of the fractured right radius of one rabbit (fig. 4 *A*) and in the distal end of the diaphysis of the left ulna in another rabbit (fig. 3 *B*) there developed lesions which were roentgenographically, grossly and microscopically indistinguishable from the giant cell tumor of man except for the portion of bone involved (to be discussed later). Also, critical study would no doubt show certain minor differences in cellular morphology. In each instance these soft, friable, vascular reddish brown masses appeared to be definitely circumscribed, to extend to the epiphysial cartilage and to bulge portions of the cortex, which in areas was extremely thin.

The tissue was only loosely attached to the cortex.

The histologic structure illustrated in figure 6 consisted typically of (1) a stroma of spindle and of round cells with large vesicular nuclei loosely disposed around numerous large blood spaces and capillaries and areas of extravasated blood and (2) giant cells containing many small oval nuclei centrally placed and of uniform size.

Thus, in two rabbits there were lesions of bone which were similar to, if not identical with, the giant cell tumor of man. The only variation, the difference in the location of the lesions, is probably more apparent

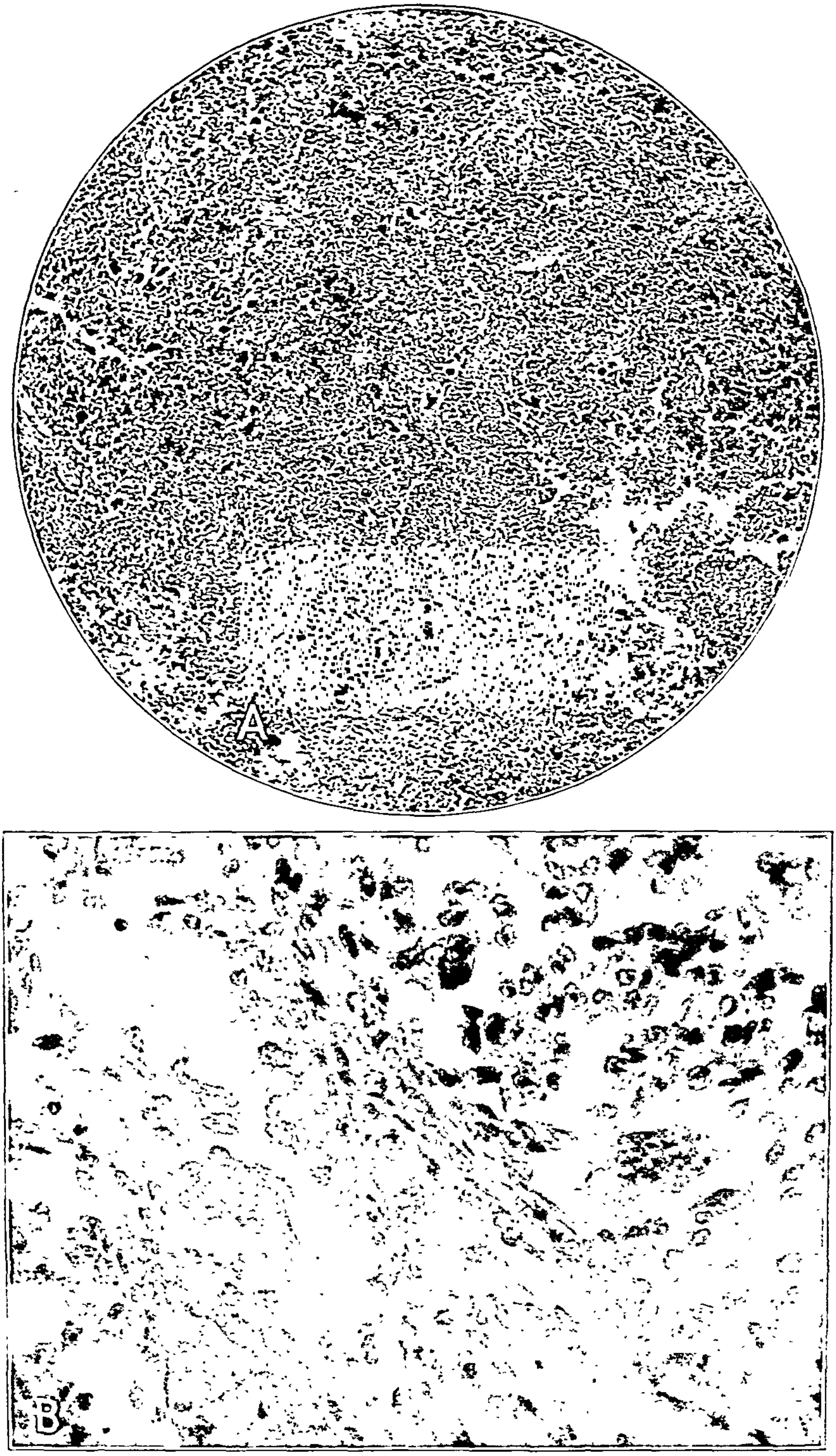

Fig. 6.—*A*, low power photomicrograph of tumor tissue removed from the distal end of the radius of rabbit 3; the tumor is shown roentgenographically in figure 4 *A*. Note the giant cells and stroma typical of a giant cell tumor. *B*, high power photomicrograph of the same tissue.

than real and can be explained on the basis of the immaturity of the animals. Whereas most giant cell tumors in man arise in or involve the epiphysis primarily rather than the metaphysis, as occurred in both rabbits, the tumor in man usually appears after the epiphysial disk has been obliterated. This cartilage was still present in the animals. That the presence of the cartilage similarly alters the location of the tumor in man has been emphasized by Peirce.[2] He stated:

> In the matter of the involvement of the "epiphyses" of the bones, as is common terminology in the older publication particularly, it is of interest that in our series, wherever the epiphyseal discs are still present, the neoplasm has not invaded the disc, being apparently restricted to the end of the diaphysis, the metaphysis, But wherever the epiphyseal disc has been obliterated by the maturity of the bone, the tumor proceeds throughout the cancellous structure to the under surface of the articulating cartilage plate.

Since these tumors did not appear in the roentgenograms taken immediately after operation and first became apparent in those made twelve weeks later, it is obvious that insult to the bone as a result of operation was responsible for their development. In the case of the tumor in the distal end of the radius it is probable that elevation of the periosteum at the time of operation and the subsequent stripping from hemorrhage deprived the distal fragment of much of its blood supply. Also as a result of trauma there was hemorrhage into the medullary portion. Thus there existed, as has been pointed out by Geschickter and Copeland,[1] circumstances conducive to the formation of a giant cell tumor. Their explanation of the process is related in the discussion which follows. In the animal in which the tumor involved the ulna it is probable that the trauma associated with epiphysial separation was the causative factor.

The abnormal association with displaced segments of cartilage in both tumors deserves consideration. It is possible that the transplanted segment of costal cartilage in the radius and the injured displaced segment of epiphysial cartilage in the ulna may have played a part in the formation of the tumors. Ewing [3] and Wright [4] have brought forth evidence of the origin of variants in giant cell tumors from absorption of aberrant islands of cartilage cells which occur not infrequently in children suffering with rickets. They suggested that this process of absorption of cartilage may give rise to neoplastic proliferation.

COMMENT ON GIANT CELL TUMOR

A discussion of the etiology of giant cell tumor involves a consideration of an old controversy into which enters four theories: (1) that the tumor is a neoplasm or blastoma, (2) that it is an inflammatory lesion on a toxic or infectious basis, (3) that it is of metabolic origin suggested by its occurrence in association with the disturbance in calcium metabolism accompanying hyperparathyroidism and (4) that it represents simply a perverted reparative process in bone in which there has been injury, with resultant hemorrhage and a disturbance of circulation.

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[2] Peirce, C. B.: Giant-Cell Bone Tumor, Am. J. Roentgenol. 28:167, 1932.

[3] Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

[4] Wright, J., cited by Kolodny.[14]

The infectious and toxic inflammatory theory has little or no evidence to support it and has been abandoned. Many early observers, among them Nélaton,[5] Paget[6] and Virchow,[7] were impressed with the lack of evidence of anaplasia and with the benign course of the tumor. This fact has constantly been emphasized by the studies of Barrie,[8] Gross,[9] Codman,[10] Bloodgood,[11] Stone and Ewing,[12] Elmslie,[13] Kolodny,[14] Geschickter and Copeland[1] and many others. From a critical review of the literature, Stone and Ewing[12] found not a single authenticated case of malignant degeneration or of dissemination of true metastases of a giant cell tumor.

There is a growing conviction, held by most students of this problem, that a giant cell tumor is merely a "chronic resorptive process" in response to trauma to bone, as suggested by Konjetzny.[15] He arrived at this conclusion from observing the histologic changes which take place in intermedullary hemorrhages, which he was able to show excited a proliferative response in bone marrow productive of the elements found in the giant cell tumor. Similar proof of the traumatic origin of this tumor has been presented by Cone[16] in his investigation of an ossifying hematoma from which he observed that "osteitis fibrosa, hemorrhagic osteomyelitis and giant cell tumor of bone have their representations in the microscopic pathology of this ossifying hematoma." Geschickter and Copeland[1] reported four cases of subperiosteal giant cell tumor in the shafts of long bones. In these cases, as in most cases of giant cell tumor, there was a history of recent trauma to the site. In the roentgenograms the following picture was observed:

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[5] Nélaton, E.: Mémoire sur une nouvelle espèce de tumeurs à myéloplaxes. Thèse de Paris, no. 58, 1860.

[6] Paget, J.: Lectures on Surgical Pathology, London, Longmans [and others], 1863.

[7] Virchows, cited by Stone and Ewing.[12]

[8] Barrie, G.: Haemorrhagic Osteomyelitis, Am. J. Surg. **35**:253, 1921.

[9] Gross, S. W.: Sarcoma of the Long Bones, Am. J. M. Sc. **78**:17, 1879.

[10] Codman, E. A.: Bone Sarcoma, New York, Paul B. Hoeber, Inc., 1925.

[11] Bloodgood, J. C.: The Conservative Treatment of Giant-Cell Sarcoma. Ann. Surg. **56**:210, 1912.

[12] Stone, W. S., and Ewing, J.: An Unusual Alteration in the Natural History of a Giant Cell Tumor of Bone, Arch. Surg. **7**:280 (Sept.) 1923.

[13] Elmslie, R. C.: Fibrocystic Disease of the Bones, in Robert Jones Birthday Volume, London, Oxford University Press, 1928, p. 127.

[14] Kolodny, A.: Bone Sarcoma: The Primary Malignant Tumors of the Bone and the Giant Cell Tumor, Chicago, Surgical Publishing Company of Chicago, 1927.

[15] Konjetzny, C. E.: Die sogenannte "lokalisierte Osteitis Fibrosa," Arch. f. klin. Chir. **121**:567, 1922.

[16] Cone, S.: Ossifying Hematoma, J. Bone & Joint Surg. **10**:474, 1928.

> . . . the periosteum is raised by a tumor casting little or no shadow and resembles a subperiosteal hematoma. At operation, an extremely thin capsule or shell of bone described by most operators as a blue dome presents itself and when incised, a cavity containing blood is found. Tissue removed from this cavity and examined under the microscope shows a structure of typical giant cell areas. . . . In these cases it is clear that trauma and hemorrhage followed by separation of the periosteum are the initial pathologic events.

Geschickter and Copeland expressed the belief that after trauma to the end of a bone there results under certain circumstances a disturbance of the normal processes of repair, "an imbalance between osteoclastic proliferation in the medulla and reactive compact bone in the cortex." They pictured the sequence of events as follows: After trauma there is a hemorrhage which separates the periosteum from the cortex and interrupts its periosteal blood supply, which in turn inhibits the normal reactive processes in the underlying cortical bone. The medullary circulation takes on increased activity in revascularizing the injured area. This takes place only after the osteoclasts have opened up channels in the bone for the budding capillaries. This increased osteoclastic activity is superimposed in an area in which injured and unnourished cortical bone is undergoing necrosis and in which osteoclasts are already unusually active in absorbing bone. "An imbalance is thus created between bone destruction by osteoclasts (and ingrowth of granulation tissue) and new bone formation that would normally proceed from the reactive cortex were its circulation intact."

Ballin and Morse[17] have explained the frequent occurrence of giant cell tumors in association with hyperparathyroidism on the basis of hemorrhage from trauma in osteoporotic bone in which there is already an imbalance. Also, this demineralized type of bone suffers insult with hemorrhage from little or no trauma.

DISTURBANCES IN GROWTH

As stated previously, separation of the distal epiphysis of the ulna took place in twelve of the twenty-eight legs on which operation was performed, and all became completely or nearly completely reduced spontaneously. In seven, the reduction was complete, and in five of these no subsequent disturbance of growth could be detected. In the remaining two and in the five which were incompletely reduced there was, by comparison with the former group, definite evidence of retardation or arrest of longitudinal growth. Since each of these epiphysial separations accompanied a break in the continuity of the companion bone, the radius, deflection deformities anteroposteriorly or laterally from unequal growth from a single epiphysis cannot be determined.

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[17] Ballin, M., and Morse, P. F.: Parathyroidism and Parathyroidectomy. Ann. Surg. **94**:592, 1931.

It is fair to conclude, however, that epiphysial separation resulted in a disturbance of longitudinal growth in 58 per cent of instances in the entire group and in 100 per cent of those in which reduction was incomplete.

CONCLUSIONS

1. In growing animals traumatic epiphysial separation in long bones often produces retardation or arrest of longitudinal growth of these bones. These disturbances in growth occurred more often in the animals in which reduction was not complete.

2. The incidental production of cartilaginous exostosis in animals and the relation of this tumor to traumatic separation of the epiphysis and to trauma to the epiphysial cartilage are reported. A suggestion of a comparable etiology in man in certain instances in ventured.

3. The production of a giant cell tumor in two animals incidental to operative trauma to bone is reported. These observations add confirmation to the traumatic and inflammatory theory of the etiology of this type of tumor.

ABSTRACT OF DISCUSSION

Dr. L. D. Smith, Milwaukee: I think that this report is extremely significant and that Dr. Bisgard's interpretation of his data is of great importance.

In this respect it may be that the following phenomena are significant: Recently I removed a four-flanged fixation spike from a healed fracture in the neck of the femur. The spike had been in place for one year. It was much more difficult to remove than to insert. The density of the bone had increased in the immediate neighborhood of the spike with increased cellular tension. I removed at the same time a Steinmann pin which had been in the bone a few days. It was very loose. The flanges of the spike were $^{64}/_{100}$ inch (1.6 cm.) thick. This thickness did not violate the histologic integrity of the adjacent bone tissue but increased the cellular tension to the point of increasing the pressure on the invading spike. The cylindric pin, because of its geometric properties, required the greatest volume of bone displacement to accommodate it with the least surface friction. Such a pin becomes loose a few hours after its insertion. In one case pressure stimulated the bone cells to greater tonicity, and in the other case it destroyed them.

In some cases of inflammation of bone there is exhibited increased growth; in others, there may be decreased growth. It seems that each phenomenon is a factor not of chemotaxis but of cellular tension, as implied by the chemical and physical phenomena.

The weird growth effects in association with displacement of either end of the radius of the ulna, the other end being intact, are well known. These discrepancies in growth in association with paralysis of the muscles are a familiar manifestation of modified cellular tension.

It is said that irritation is a prolific source of neoplastic growth. It may be that it is a primary phenomenon of cellular tension. It is of interest that Hastings and Eichelberger (The Exchange of Salt and Water Between Muscle and Blood: I. The Effect of an Increase in Total Body Water Produced by the Intravenous Injection of Isotonic Salt Solutions, *J. Biol. Chem.* **117**:73 [Jan.] 1937; cited in The Exchange of Salt and Water Between Muscle and Blood, editorial, *J. A. M. A.* **108**:1893 [May 29] 1937) have observed that an excess of fluid may result in an increase in intracellular fluids without a change in the cell volume.

It has been found in a consideration of the reaction of the erythrocytes in man to dextrose that whereas chemical methods indicate a rapid absorption of dextrose the changes in volume observed by the hematocrit method do not (Luck, J.: Annual Review of Biochemistry, Stanford University Press, Stanford University, Calif., 1935, vol. 4). It is not improbable that physiologic adaptive, compensatory changes in chemical tension are constantly taking place with an attendent change in cellular tension but without a change in the cell volume. This necessarily alters the vibratory frequency of the structure and of the tissue of which it is a part and therefore may be a function of wave phenomena of activated muscle.

It does seem that the phenomenon of cellular tension is an important or essential factor in the growth of tissue. Carey (Studies in the Dynamics of Histogenesis, *Radiology* **13**:1 [July] 1929) has clearly shown the effect of external tension on the growth of bone by the action of muscles. Cellular tension may be either intrinsic or extrinsic and physiologic or uncontrolled. It may be that the interesting observations of Dr. Bisgard demonstrate a phenomenon of disorderly and uncontrolled cellular tension and that the phenomenon of neoplastic growth is related to cellular tension.

CAVERNOUS HEMANGIOMA OF THE SPLEEN

REPORT OF A CASE AND REVIEW OF THE LITERATURE

LEWIS E. SCHOTTENFELD, M.D., C.M.
AND
WILLIAM L. WOLFSON, M.D.
BROOKLYN

Hemangioma of the spleen is rare. This is manifested by the paucity of the literature on the subject and by the fact that Lubarsch reported only three angiomas of the spleen in 19,000 autopsies. The records of the Jewish Hospital yielded data on five cases of cavernous hemangioma of the spleen. The case on which this report is based was one in which a large hemangioma was removed surgically, while in the other four small hemangiomas were discovered at necropsy which had given no symptoms during life. This gives an incidence of 0.14 per cent in 2,800 autopsies.

As a preliminary statement, it might be said that in the past much confusion has existed in the use of the terms angioma and endothelioma and of combinations of these. For the purpose of this paper angioma and endothelioma are employed to denote benignancy.

Hoge[1] in 1895 discussed the pathologic structure of hemangiomas in his report of a case in which operation was performed, with complete recovery. Homans[2] in 1897 cited a case in which 38 quarts (36 liters) of bloody fluid was removed by five paracenteses in one year. At operation the tumor was extirpated without removing the spleen. The symptoms recurred; reoperation resulted in the death of the patient. Huntington[3] aspirated cystic fluid and marsupialized the sac of a splenic tumor which contained blood. The summary of seventy-two cases of splenic cysts reported up to 1912 by Fowler[4] is a classic for completeness and thoroughness. Dowd[5] analyzed a series of fourteen cases reported by others and included the report of a case of his own. Jopson's[6] patient lost 100 pounds (45.4 Kg.), and she complained of a pain and a mass in the left upper quadrant of the abdomen. She made an unevent-

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From the Surgical Service and Department of Pathology, Jewish Hospital of Brooklyn.

1. Hoge, M. D.: M. Rec. **48**:418, 1895.
2. Homans, J.: Ann. Surg. **25**:732, 1897.
3. Huntington, T. W.: Tr. Am. S. A. **25**:366, 1907.
4. Fowler, R. H.: Ann. Surg. **57**:658, 1913.
5. Dowd, C. N.: Ann. Surg. **62**:177, 1915.
6. Jopson, J. H.: S. Clin. North America **1**:235, 1921.

ful recovery after splenectomy. Thirty-three angiomas were found in one spleen in a case reported by Müller.[7] Smith and Rusk[8] summarized ninety-seven cases of angiomas and endotheliomas reported in the literature, discussed their possible pathogenesis and classified them under five headings. Moschcowitz,[9] Krumbhaar and Scott[10] and Orlandi[11] contributed to the literature. Wright's case[12] was one of malignant hemangioma of the spleen. Schwarz[13] emphasized the dangers which might follow any procedure other than splenectomy. Zeno and Cid[14] removed a spleen with a lesion reported as hemangio-endothelioma and presented a thorough study of the case. An abscess within a hemangioma of the spleen accounted for the intermittent fever in the case reported by Kellert.[15] Haines and McIlroy's[16] patient, who had an angioma of the spleen, complained of indigestion over a long period, followed by sudden pain, prostration, vomiting and tenderness. Hematoperitoneum and a ruptured spleen were found at operation. The patient died forty-eight hours later.

Other cases have been reported in which no striking features were presented.

PATHOLOGY AND PATHOGENESIS

The cavernous angioma first appears as a circumscribed tumor, developing often on the basis of a congenital nevus, and tends to enlarge steadily over a period of many years. It may be observed at birth or may begin to appear at any age. It may occur anywhere in the body. When allowed to progress, the growth may attain very large dimensions. The course of the tumor is slowly progressive, and it enlarges by distention of the original vessels and by the formation of new vessels. Free anastomosis with large arteries or veins may become established, and severe or fatal hemorrhage may occur. Spontaneous regression may result from contraction of the capsule, thrombosis or inflammation, or a cure may be affected by continuous pressure on the tumor or vessels leading to the tumor.

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[7] Müller, H.: Virchows Arch. f. path. Anat. **238**:76, 1922.

[8] Smith, C. E., and Rusk, G. Y.: Endothelioma of Spleen: Study of Two Cases, with Review of Literature of Primary Malignancy of Spleen, Arch. Surg. **7**:371 (Sept.) 1923.

[9] Moschcowitz, E.: Am. J. M. Sc. **131**:675, 1906.

[10] Krumbhaar, E. B., and Scott, J. P.: S. Clin. North America **7**:61, 1927.

[11] Orlandi, N.: Virchows Arch. f. path. Anat. **269**:152, 1928.

[12] Wright, A. W.: Am. J. Path. **4**:507, 1928.

[13] Schwarz, F.: Beitr. z. klin. Chir. **150**:130, 1930.

[14] Zeno, A., and Cid, J. M.: Ann. d'anat. path. **7**:583, 1930.

[15] Kellert, E.: Am. J. Cancer **16**:412, 1932.

[16] Haines, C. E., and McIlroy, P. T.: Spontaneous Rupture of Cavernous Angioma of Spleen, J. A. M. A. **100**:1862 (June 10) 1933.

The pathogenicity of the cavernous angioma is not complex. It consists of a meshwork of fine fibrous connective tissue of different thicknesses which encloses blood filled sinuses of varying sizes and shapes. In the simple hemangioma the connective tissue is noncellular, almost hyalinized. Where these channels are lined by endothelial cells, abnormal and active proliferation of these cells may give rise to a malignant endothelioma.

Hemangioma is a tumor composed of newly formed blood vessels. Opinions as to the origin and growth of such a tumor vary considerably. By means of interstitial injection, Ribbert found that the vessels in the simple hemangioma have few or no lateral anastomoses, from which he concluded that the tumor process is present in an isolated segment of the wall of the vessel and produces elongation and varicosities in a more or less closed territory. The real origin of the hemangioma must be referred to a developmental anomaly in the structure of certain vascular segments which do not fit into the circulatory system and which retain embryonal characters. The congenital origin of the great majority of hemangiomas speaks strongly in favor of a tissue predisposition as a prominent factor in their genesis.

When the vascular channels which comprise the tumor are widely dilated and the connective tissue septums are thin, the angioma is designated as cavernous. Some of these tumors pulsate. Thrombosis and calcific phleboliths may occur in dilated sinuses.

Ewing[17] names these tumors *hemangioma simplex* and divides them into (1) the common naevus venosus, or telangiectasis of the skin, congenital in origin, (2) the subcutaneous angiomas of children, with local invasion of the underlying structures, and (3) the hyperplastic type of hemangioma hypertrophicum, which grows rapidly and has a poor cellular differentiation. This group he subdivides into (*a*) the capillary type and (*b*) the cavernous type.

When one considers the histologic make-up of the spleen, one finds that from each component of the splenic architecture there can arise a different type of splenomegaly. Fibromas and fibrosarcomas may develop from the capsule and trabeculae; lymphadenomas and lymphosarcomas may originate from the lymphoid elements; angiomas, cavernous angiomas and endotheliomas may be derived from the vascular or sinus endothelium. A cavernous angioma of the so-called benign type may be potentially malignant; the possibility of Ewing's hyperplastic cavernous angioma becoming a malignant endothelioma deserves consideration. Pool and Stillman,[18] in their monograph on "Surgery of the Spleen," stated that the presence of angiomas in organs other than the spleen does not necessarily indicate that the growths are metastatic from the spleen, since it is well known that angioma may exist as multiple lesions.

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[17] Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

[18] Pool, E. H., and Stillman, R. G.: Surgery of the Spleen, New York, D. Appleton and Company, 1923.

After studying the reports of fifteen cases of angioma of the spleen by Smith and Rusk in 1923, only eleven cases with reasonably complete histories have been selected by us for analysis. These, together with the five cases reported after 1923 by others, are as follows:

Smith and Rusk	up to 1923	11 cases
Wright	1928	1 case
Schwarz	1930	1 case
Zeno and Cid	1930	1 case
Kellert	1932	1 case
Authors' case	1933	1 case
		16 cases

The ages of the patients in this series ranged from 1½ years to 56 years. Viewed in decades, the ages are as follows:

Decades	No. of Patients
1-10	1
11-20	3
21-30	2
31-40	3
41-50	2
51-60	4
Not stated	1

Males and females were equally affected. There was one case in this group in which an angioma occurred during pregnancy. In females the occurrence of splenic tumors during the child-bearing period has been noted by Monnier, who explained that during the menses, pregnancy and the menopause there is an engorgement of the spleen. This observation has been corroborated by operations during pregnancy. In three cases in the series there was some form of injury as a possible factor in the development of the tumor. The presence of some toxic or infective agent may predispose the spleen toward the development of angiomas. Chronic malaria predominates in this respect. In two of the sixteen cases here reported there was a history of chronic malaria. The pathogenicity in malaria may offer some explanation for this development. In cases of malaria the spleen is enlarged and soft, and the capsule is thickened and adherent to the surrounding tissues. The pulp is hyperplastic, and the fibrous tissue trabeculae are markedly ickened. With such a foundation it may be understood how either ontaneously or due to trauma a splenic tumor of the angiomatous type ay develop.

SYMPTOMATOLOGY

The symptoms presented by the patient are not all uniform. Only e larger cysts and tumors give rise to symptoms; the small ones often not manifest themselves clinically. The symptoms may be the result peritoneal reaction due to a low grade inflammation around the capile which produces adhesions, causes pain and fever and sometimes duces vomiting. The duration of symptoms varied greatly. In the llected series this ranged from two days to five years. The majority patients had noted some disturbance from four to eight months before eking medical aid. In most instances it was a tumor mass alone or ith pain which gave the first information that the normal status of the atient had changed.

It is interesting to analyze and study the incidence of the various gns and symptoms which were found in this series of cases of cavernus angioma. In the order of their frequency they are as follows:

	No. of Cases	Percentage
Tumor	16	100.0
Pain	10	62.5
Secondary anemia	2	12.5
Ascites	2	12.5
Loss of weight	3	18.7
Fever	2	12.5
Asthenia	3	18.7
Dyspnea	2	12.5
Jaundice	2	12.5
Leukocytosis	1	6.2
Chills	1	6.2
Constipation	1	6.2
Leukopenia	1	6.2
Pruritus	1	6.2

A mass, confirmed by examination, was by far the outstanding complaint offered by the patient. The sizes of the tumors varied. They were situated in the left side of the hypochondrium, the epigastrium or the middle of the abdomen or projected toward the left lumbar region. A tumor may be fixed or movable, smooth or irregular, firm or elastic, depending on the density of the adhesions to the surrounding organs, whether the tumor is solid, cystic or multilocular, on the amount of retraction due to fibrous connective tissue and on the tension of any cystic contents of the tumor.

Pain manifested itself in various ways. It was sharp or pressurelike or gave a sensation of heaviness or dragging. It was usually present in the left upper quadrant of the abdomen and in the epigastrium. Symptoms of pressure produced by the large splenic tumors were evidenced by digestive disturbances, such as constipation or diarrhea. A definite complaint of pain occurred with most large splenic tumors. It was present in 62.5 per cent of the group. Monnier mentioned a friction rub heard in some cases, which was due to perisplenitis.

Weakness and loss of weight were named as complaints in 18.7 per cent of the cases.

In 12.5 per cent of the group the following symptoms were found: anemia, ascites, dyspnea, fever and jaundice. Secondary anemia was possibly due to some direct effect of the angioma on the hematopoietic system, of which the spleen forms an integral part. This in some way may have influenced the hemolysis of the red blood cells or inhibited hyperplasia of the bone marrow. Ascites may become excessive and cause discomfort. Abdominal paracentesis was repeatedly performed in Homan's case for this reason. Necrosis or thrombosis within the spleen or splenic tumor or in the splenic veins may be the cause of the elevation in temperature. Secondary infection was also recorded and resulted in one case in the formation of an abscess. Dyspnea occurred when a large cavernous angioma of the spleen impinged on the diaphragm, compressed the lungs and reduced the respiratory effort and the vital capacity. The pathogenesis of jaundice, although not stated, can easily be comprehended because of the high incidence of metastasis to the liver with biliary obstruction.

More infrequently, in 6.2 per cent of the cases, there was leukocytosis, leukopenia, chills, pruritus or constipation. The occurrence of chills with or without a cellular response in the blood was in all probability due to the invasion of the blood stream with small emboli, either bacterial or necrotic material from the tumor, which so closely borders on the blood vessels of the spleen.

METASTASIS

The liver was the seat of angioma in six cases of the series. The lesion was also found in single instances in the lymph nodes, pancreas, stomach and intestines, lungs and pleura and in the vertebrae. Whether these lesions were true metastases or occurred concomitantly with the angiomas of the spleen was not definitely cited. In the liver the lesion was probably an extension from the splenic vein through the portal system. When the stomach and intestines were involved, the spread probably occurred by contiguity, because dense adhesions intervened between the splenic tumor and the stomach. The sites of metastases were as follows:

	No. of Cases	Percentage
Lymph nodes	1	6.2
Liver	6	37.5
Pancreas	1	6.2
Stomach and intestine	1	6.2
Lungs and pleura	1	6.2
Vertebrae	1	6.2

DIAGNOSIS

Before operation the diagnosis of a primary hemangioma of the spleen is difficult. An angioma may be considered when there is a history of a previous malarial infection, trauma or pregnancy followed at some variable time by a tumor in the left side of the hypochondrium or the epigastrium. A diagnosis may be more suggestive when there is pain, loss of weight, asthenia, secondary anemia, ascites or fever associated with the tumor. The presence of a metastasis to the liver, when large enough to be palpated, may be helpful.

It is necessary to differentiate by clinical and roentgenographic investigation a large lesion of some other organ from a splenic tumor. A cyst of the omentum, mesentery, pancreas or left lobe of the liver, although rare, must be considered. An enlarged kidney, due to any of various causes, cystic, inflammatory or neoplastic, may be displaced from the lumbar fossa posteriorly to occupy a more anterior position. A neoplasm of the splenic region of the colon is occasionally of such size that it must be distinguished from one of the splenic organ. A pedunculated ovarian cyst that ascends from the pelvic region toward the left lumbar and upper abdominal quadrant must be thought of. A retroperitoneal tumor may attain enormous dimensions and cause some confusion in diagnosis.

TREATMENT

In Fowler's summary of the treatment in seventy-two cases reported up to 1912 it was found that surgeons up to that time had treated cavernous hemangioma of the spleen (1) by puncture, (2) by incision and drainage of the tumor mass with marsupialization of the tumor sac, (3) by excision of the tumor and (4) by splenectomy. Splenectomy was the operation of choice in twenty-five (34.7 per cent) of the seventy-two cases and yielded the best results.

Operation was performed in fourteen of the sixteen cases which form the basis of this study. In twelve the entire spleen was removed, in one a partial splenectomy was done and in another the spleen was left in situ after an exploratory operation on the abdominal cavity.

The remaining two cases of the series were fatal, and at necropsy a hemangioma was found. In one of these, angiomas were found in other organs. Of thirteen cases in which the spleen was either totally or partially removed, cure was obtained in ten. Death occurred in two cases shortly after the operation and in one four weeks later. In the remaining case, in which an exploratory operation was done, death occurred sixty hours later. Thus, 62 per cent of the patients in this series who were subjected to splenectomy were cured. The operative mortality was 21.4 per cent; included in this estimate of mortality are the two cases in which death occurred immediately after the operation and the one in which death occurred sixty hours later. The case in which death occurred four weeks later cannot be considered one of "operative death." Early splenectomy is urged in cases of cavernous hemangioma of the spleen. Otherwise certain dangers may be anticipated, such as spontaneous rupture, fatal hemorrhage or malignant transformation, as pointed out by Schwarz.[13]

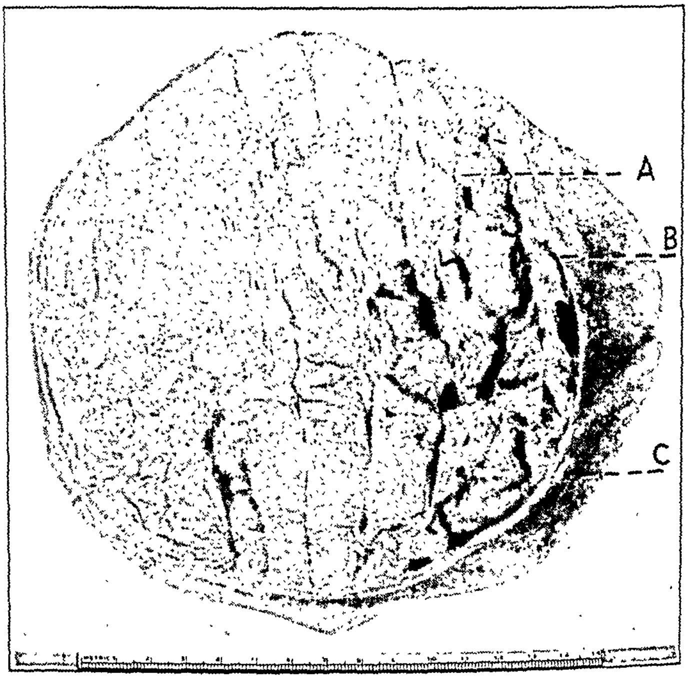

Fig. 1.—Gross specimen of a hemangioma of the spleen. *A* indicates the hemangioma, *B*, the capsule of the tumor, and *C*, splenic tissue.

REPORT OF CASE

History.—D. B., a white woman aged 31, was admitted to the Jewish Hospital on Dec. 21, 1933, to the service of Dr. William L. Wolfson. She complained of a large swelling in the left upper quadrant of the abdomen, which had been present for seven years. The mass had grown steadily larger. Ten weeks prior to admission she had twinges of pain over the region of the tumor. There had been no loss of weight, strength or appetite during the past seven years. No abnormal digestive or urinary symptoms were presented. No prolonged bleeding was noted during the menstrual periods or after any minor injuries.

The family history and the past history were irrelevant.

Physical Examination.—The patient appeared well nourished, of good color and not acutely ill. Both pupils were equal and reacted to light and in accommodation. The heart and lungs were normal. The left upper quadrant of the abdomen was noticeably prominent. A tumor, firm, smooth and tender, occupied the entire left side of the hypochondrium and the left lumbar region. The liver and kidneys were not enlarged.

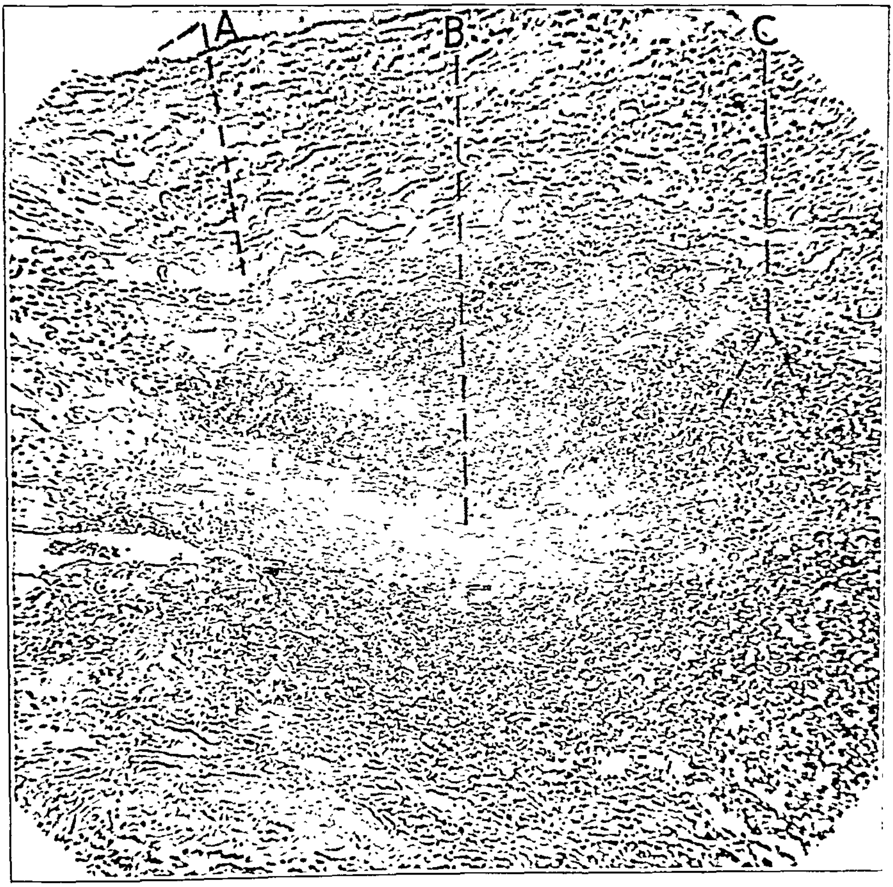

Fig. 2.—Low power photomicrograph of the hemangioma of the spleen. *A* indicates blood filled sinuses; *B*, hyalinizing connective tissue stroma, and *C*, red blood cells.

The temperature was 99.4 F., the pulse rate 90 per minute and the respiratory rate 20 per minute. The systolic blood pressure was 124 mm. of mercury and the diastolic pressure 90 mm. Urinalysis gave negative results. The red blood cell count was 3,400,000, and the hemoglobin content 63 per cent (Dare). The leukocyte count was 7,800 with 65 per cent polymorphonuclear cells (band forms, 5 per cent), 4 per cent eosinophils, 2 per cent basophils, 27 per cent lymphocytes, and 2 per cent monocytes. There were slight anisocytosis and poikilocytosis. Some oligochromasia was present. The fragility test showed that hemolysis began with a concentration of sodium chloride of 0.42 per cent and was complete with 0.30 per cent. Chemical analysis of the blood showed: sugar, 154 mg. per hundred cubic centimeters of blood; creatinine, 1.2 mg.; urea nitrogen, 11.2 mg., and uric acid, 5 mg. The carbon dioxide-combining power was 49.7 volumes per hundred cubic centimeters of blood.

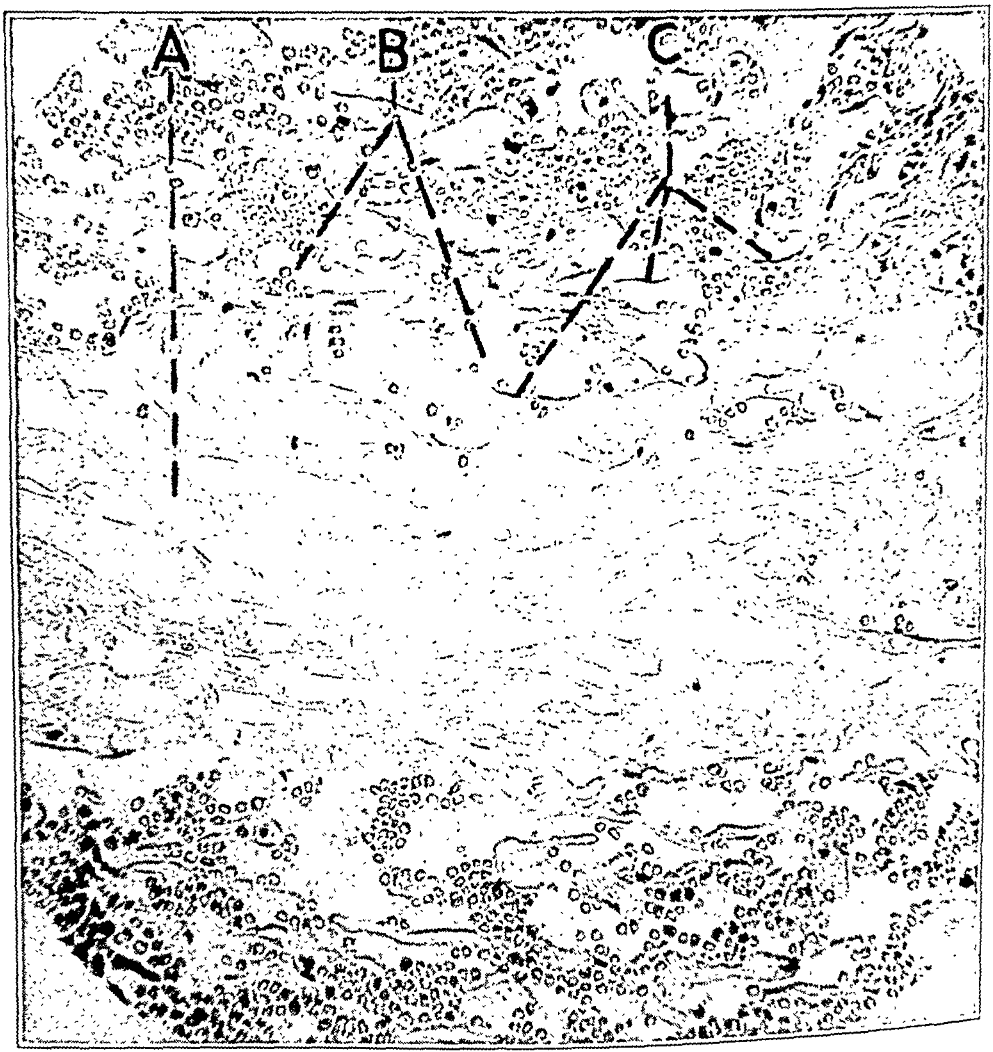

Fig. 3.—High power photomicrograph of the hemangioma of the spleen. *A* indicates hyalinizing connective tissue stroma; *B*, blood sinuses, and *C*, endothelial cells lining the sinuses.

A study of the pneumoperitoneum disclosed a large tumor in the left side of the hypochondrium, the borders of which were smooth and not adherent. Inferiorly it was limited by the lienorenal ligament. The mass was about the size of a Cassawba melon and was splenic in origin.

The patient was given a transfusion of blood the day before the operation.

Operation.—Through an upper left rectus incision into the abdominal cavity there was disclosed a large red-brown spleen, which was smooth on the surface.

A major part of it extended from beneath the left costal margin toward the middle of the abdomen. On the outer surface there was a large plaquelike area the size of a small saucer, distinctly discolored, yellowish white and slightly raised above the general surface. Beneath this area the splenic pulp was mushy and almost cystic. The spleen was singularly clear of adhesions and was readily dislocated forward and upward. The liver, ovaries and kidneys were normal. A splenectomy was easily performed. The abdominal wound was closed without drainage.

The patient was discharged thirteen days after operation. When last seen, on May 22, 1935, she was perfectly well. The abdominal wound was entirely healed.

Pathologic Report (Dr. Max Lederer).—The spleen measured 21 by 18 by 10 cm. (fig. 1). The major part was whitish, and the rest was the color of a normal spleen. The entire surface was somewhat dull. The consistency was semisolid. On section, it was composed of a small rim of compressed splenic tissue, whereas the remainder was occupied by an encapsulated circumscribed mass of yellowish and brown tissue. This mass measured 16.5 cm. in diameter. The consistency of the mass in some parts was rather firm and in other parts gelatinous. On sectioning the yellow masses of tissue, numerous spaces were disclosed with clear and pink fluid. The capsule was composed of a thick hyalinized mass, which was rough and contained areas of calcific deposits.

Microscopic Examination (fig. 2).—The encapsulated mass showed almost entirely necrotic and degenerated tissue. In many places there was a network of trabeculae forming irregularly sized and shaped spaces, which contained both fresh and old blood. These trabeculae in some places were very delicate; in others they consisted of broad bands of connective tissue. The nuclear elements had completely disappeared. Thrombi were seen in the larger spaces. The capsule was made up of a lamellated mass of hyaline tissue containing numerous spaces and deposits of calcium (fig. 3). The remaining splenic tissue, except for areas of compression, was normal. The diagnosis was hemangioma of the spleen with degenerative changes.

SUMMARY

A case of cavernous hemangioma of the spleen with successful treatment by splenectomy is recorded.

A review of the literature on cavernous hemangiomas of the spleen is briefly outlined, with an analysis and discussion of the clinical and pathologic aspects.

EXPERIMENTAL SUBTOTAL LIGATION OF THE ARTERIES SUPPLYING THE LIVER

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AND
JOSEPH POST, M.D.
CHICAGO

It was found that subtotal removal of the arterial supply of the liver in the dog was possible by means of multiple stage operations, a procedure which was fatal when carried out at one sitting.

The liver, lungs and placenta may be set apart from the other organs of the body since they receive blood of two different compositions, based on the oxygen and the carbon dioxide content. The relative contributions of the hepatic artery and the portal vein to the circulation of the liver, as well as the total flow of blood through the liver, have been estimated. The total amount of blood flowing through the liver per gram of liver per minute has been found by various investigators to be from 0.43 to 0.7 cc.,[1] from 0.46 to 1.12 cc.,[2] 0.25 cc.,[3] 0.84 cc.,[4] from 0.63 to 1.44 cc.,[5] and 0.75 cc.[6] The percentage of the circulation of the liver contributed by the hepatic artery has been found to be from 12 to 25 per cent,[1] from 20 to 25 per cent,[7] from 12.6 to 24.5 per cent,[2] 30 per cent,[4] and from 26 to 32 per cent.[5]

The question arose whether the liver could survive on blood from the portal vein when deprived of the major amount of its arterial blood supply.

REVIEW OF THE LITERATURE

An extensive literature exists on ligation of the hepatic arteries.[8] Haberer established three criteria which have removed many of the pitfalls in the investigation of this subject present in the older reports. They are as follows: (1) The point of ligation should be accurately stated, (2) the experiment should be terminated with arterial injection

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From the Department of Surgery of the University of Chicago.

[1] Grab, W.; Janssen, S., and Rein, H.: Ztschr. f. Biol. **89**:324, 1929.

[2] Blalock, A., and Mason, M. F.: Am. J. Physiol. **117**:328, 1936.

[3] Schmid, J.: Arch. f. d. ges. Physiol. **125**:527, 1908.

[4] Burton-Opitz, R.: Quart. J. Exper. Physiol. **3**:297, 1910; **4**:93, 1911.

[5] MacLeod, J. J. R., and Pearce, R. G.: Am. J. Physiol. **35**:87, 1914.

[6] Barcroft, J., and Shore, L. E.: J. Physiol. **45**:296, 1912.

[7] Schwiegk, H.: Arch. f. exper. Path. u. Pharmakol. **168**:693, 1932.

[8] (*a*) Haberer, H.: Arch. f. klin. Chir. **78**:557, 1905. (*b*) Narath, A.: Deutsche Ztschr. f. Chir. **135**:305, 1916. (*c*) Cameron, G. R., and Mayes, B. T.: J. Path. & Bact. **33**:799, 1930.

to establish collateral circulation and (3) the operation should be done with asepsis. The anatomic relationships of the hepatic artery in the dog, the cat and man are essentially similar, and the experimental findings reported in the literature may be summarized as follows on the basis of the point of ligation:

1. Acute ligation of the hepatic artery proximal to its junction with the gastroduodenal artery (fig. 1, *1*). The operation on dogs was compatible with life; no changes were found in the liver.[9] The results obtained on rabbits were similar to those obtained on dogs.[10]

2. Acute ligation of the hepatic artery proximal to its junction with the right gastric artery (fig. 1, *2*). No changes were observed in dogs.[11]

3. Acute ligation of the hepatic artery distal to the entrance of the right gastric artery (fig. 1, *3*). Haberer[8a] found that all animals except a few with large phrenic arteries died in from one to three days after operation with hepatic necrosis; in those that survived the liver was normal. Other observers found that death always occurred within a few days,[12] and others, that the operation was always fatal, with terminal hypoglycemia[13] which was not relieved by the administration of epinephrine and was caused by complete absence of glycogen in the liver, heart and skeletal muscles.[14] Some workers found the operation compatible with life and have seen no appreciable changes in the liver.[15] (In the experiments of Janson the point of ligation was not accurately described.) Many observers found that in the rabbit, provided there was no accessory artery, necrosis, liver infarcts and death usually occurred within six days.[16]

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[9] (*a*) Putzu, F.: Arch. ital. di chir. **37**:483, 1934. (*b*) Livierato, S.; Vagliano, M., and Dervenaga, A.: Ann. d'anat. path. **12**:787, 1935. (*c*) Behrend, M.; Radasch, H. E., and Kershner, A. G.: Comparative Results of Ligation of Hepatic Artery in Animals: Its Application to Man, Arch. Surg. **4**:661 (May) 1922. (*d*) Haberer.[8a]

[10] Cameron and Mayes.[8c] Putzu.[9a] Behrend, Radasch and Kerschner.[9c]

[11] (*a*) Whipple, G. H., and Sperry, J. A.: Bull. Johns Hopkins Hosp. **20**: 278, 1909. (*b*) Haberer.[8a] (*c*) Putzu.[9a]

[12] Narath.[8b] Livierato, Vagliano and Dervenaga.[9b]

[13] Collens, W. S.; Shelling, D. H., and Byron, C. S.: Am. J. Physiol. **78**: 349, 1926.

[14] Collens, W. S.; Shelling, D. H., and Byron, C. S.: Am. J. Physiol. **79**: 689, 1927.

[15] (*a*) Janson, C.: Beitr. z. path. Anat. u. z. allg. Path. **17**:505, 1895. (*b*) Whipple and Sperry.[11a]

[16] Loeffler, L.: Factors Determining Necrosis or Survival of Liver Tissue After Ligation of Hepatic Artery, Arch. Path. **21**:496 (April) 1936. Steckelmacher, S.: Beitr. z. path. Anat. u. z. allg. Path. **57**:314, 1913. Cohnheim, J., and Litten, M.: Virchows Arch. f. path. Anat. **67**:153, 1876. Cameron and Mayes.[8c] Putzu.[9a] Janson.[15a] Behrend, Radasch and Kershner.[9c]

4. Acute ligation of a branch of the hepatic artery to the liver (fig. 1, *4*). Haberer[8a] found the operation usually well borne by the dog; two animals died of peritonitis. Putzu[9a] found minimal hepatic changes compatible with life. Necrosis always occurred in the rabbits.[17]

The chief difference between the dog and the rabbit occurs in ligation of the branches of the hepatic artery, owing to a difference in the collateral circulation. The site of acute ligation is important in determining the course.

5. Ligation of the hepatic artery in stages. Haberer ligated the common hepatic and gastroduodenal arteries in one dog and one cat (fig. 1, *1* and *2*); one month later the branches to the liver distal to the preliminary ligation were ligated (*3*). The dog survived these operations, but the cat died in ten hours. Livierato and his colleagues[9b] ligated the hepatic artery in dogs (fig. 1, *1*) and subsequently removed this structure at the porta, as was done in our experiments. Their dogs survived from four to six days after the last operation and appeared normal.

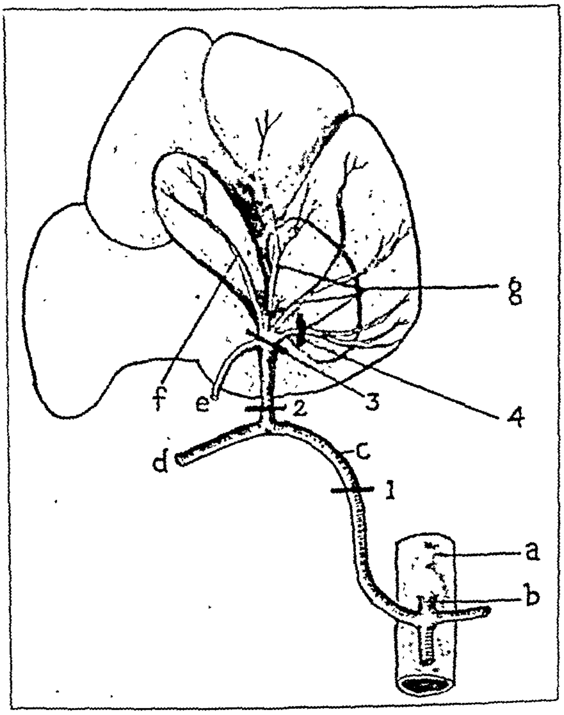

Fig. 1.—Diagram of the arterial supply to the liver of the dog: *a*, the aorta; *b*, the celiac axis; *c*, the common hepatic artery; *d*, the gastroduodenal artery; *e*, the right gastric artery; *f*, the cystic artery; *g*, the branches of the hepatic artery to the liver.

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[17] Haberer.[8a] Cameron and Mayes.[8c] Putzu.[9a]

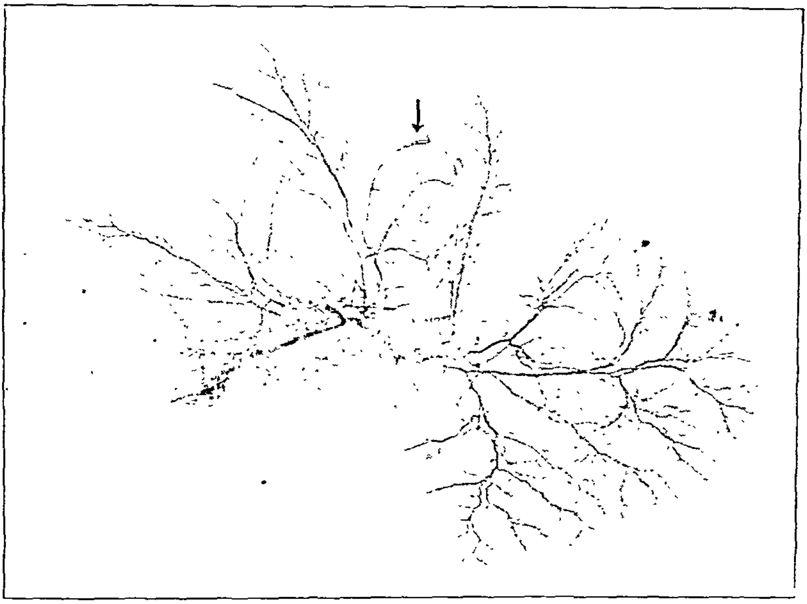

Fig. 2.—The arterial system of the liver of a normal dog. Barium sulfate-acacia solution was injected at a pressure of 200 mm. of mercury through the thoracic aorta. A fine wire encircles the gallbladder (see arrow).

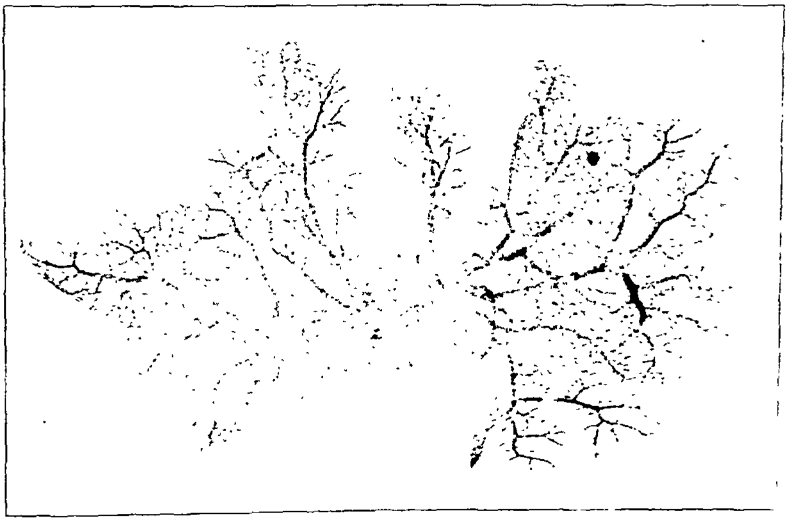

Fig. 3.—The portal system of a normal dog. Barium-acacia solution was injected through the portal vein.

EXPERIMENTAL DATA

All operations were done with the animals under ether anesthesia with asepsis.

Experiment 1.—*Acute ligation of the hepatic artery and its principal collaterals, the right gastric and gastroduodenal arteries* (fig. 1, *3*).

The arteries just mentioned were doubly ligated and sectioned between the ligatures in nine dogs. In each case a fatal result occurred: Seven dogs with the typical symptoms of liver autolysis died within seventy-two hours, and the others, at seven and twelve days (table 1). Peritonitis was present in each animal, and usually there was bloody fluid in the peritoneal and pleural cavities, as described by Haberer,[8a] in association with hepatic necrosis.

Table 1.—*Results of One Stage Ligation of the Hepatic, Gastro-Duodenal and Right Gastric Arteries in Dogs*

Dog No.	Operation	Survival Time	Course	Pathologic Picture
1	Ligation of hepatic, gastroduodenal and right gastric arteries	<24 hr.	Great postoperative thirst and vomiting; pulse rate 140; temp. 40 C. (104 F.)	Bloody fluid in peritoneal and pleural cavities; severe central hemorrhage but no inflammatory reaction in liver
2	Same as on dog 1	<24 hr.	....	No free fluid in peritoneal cavity; liver swollen and red
3	Same as on dog 1	20 hr.	Great thirst and vomiting; temp. 39.2 C. (102.2 F.)	No free fluid; liver friable and swollen; mottled areas of infarction
4	Same as on dog 1	33 hr.	Moderate vomiting; temp. 37-38.2 C. (98.6-100.8 F.); slight glycosuria; terminal convulsions (blood dextrose 39.6 mg. per 100 cc.) and blood concentration	Bloody fluid in peritoneal and pleural cavities; liver swollen and very red; mostly normal on histologic examination except for central hemorrhage and areas of coagulation necrosis
5	Same as on dog 1	7 days	Bradycardia (pulse rate 68-80) for 24 hr.; dog seemed normal for 6 days	Bloody fluid in peritoneal and pleural cavities; liver very red and friable
6	Same as on dog 1	12 days	No fever for 2 days; blood dextrose normal (86 mg. per 100 cc.); died of perforation of gallbladder	Bloody fluid in peritoneal and pleural cavities; liver grossly and microscopically normal
7	Ligation of hepatic and gastroduodenal arteries	24 hr.	....	Bloody fluid in peritoneal cavity; liver very swollen and red with patches of necrosis
8	Same as on dog 7	40 hr.	In good condition for 30 hr.	Sponge liver; extensive necrosis
9	Same as on dog 1 plus ligation of common bile duct	<72 hr.	Temp. 36.5-38 C. (97.9-100.4 F.); much thirst and vomiting; bile and albumin ++++ in urine; blood dextrose 51.3 mg. per 100 cc.	Purulent peritoneal fluid; liver very red with necrotic areas

Experiment 2.—*Subtotal removal of the arterial supply to the liver. Preliminary ligation of the hepatic artery proximal to its communication with the gastroduodenal artery. Subsequent excision of the hepatic arteries at the porta hepatis and subsequent ligation of the phrenic arteries.*

In the earlier experiments the hepatic artery was gradually compressed with a metal clamp devised by Goldblatt and his co-workers,[18] but for these purposes

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[18] Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: J. Exper. Med. **59**:347, 1934.

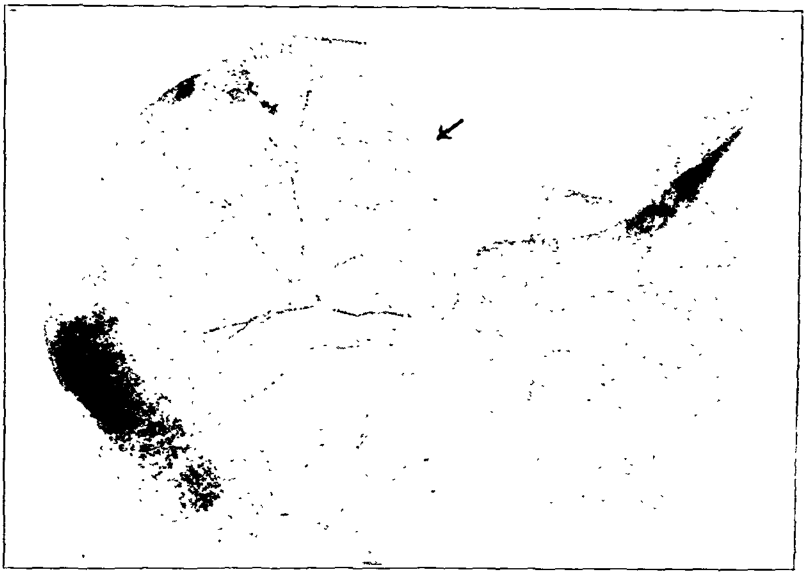

Fig. 4.—The arterial system of the liver of a dog after removal of the hepatic artery and ligation of the right gastric, gastroduodenal, cystic and left phrenic arteries (table 2, dog 7). Barium-acacia solution was injected through the aorta. The right phrenic supply may be seen. The arrow points to the gallbladder.

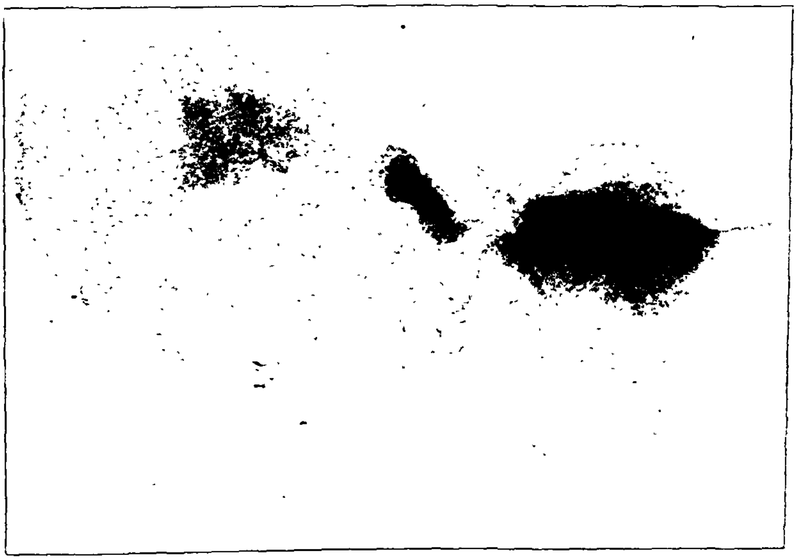

Fig. 5.—The arterial system of the liver of a dog after subtotal arterial removal (table 2, dog 5). Barium-acacia solution was injected through the aorta at a pressure of 200 mm. of mercury.

a double ligature of the hepatic artery (fig. 1, *1*) with section was more efficient and was used exclusively in later experiments. From one to four weeks later the gastroduodenal and right gastric arteries were doubly ligated, and the hepatic artery was dissected and excised and its branches ligated where they entered the liver; about 2 cm. of the cystic artery was removed with the entire hepatic artery and 2 cm. of each of the individual branches to the liver.

TABLE 2.—*Results of Multiple Stage Ligation of Hepatic Artery and Its Principal Collaterals in Adult Dogs*

Dog No.	Operation	Course	Pathologic Picture	Comment
1	Hepatic artery two-thirds occluded at 0 days; completely occluded* after 22 days; ligation of right gastric and gastroduodenal arteries after 33 days	Gained weight; active; appeared normal; killed after 92 days	Gallbladder shrunken, increased fibrosis; fatty infiltration of liver (++); area of round cell infiltration (+)	Hepatic artery not excised
2	Right gastric and gastroduodenal arteries excised at 0 days; hepatic artery three-fourths occluded* after 11 days and ligated after 33 days	Appeared normal; killed after 62 days	No changes in liver or gallbladder	Hepatic artery not excised
3	Right gastric and gastroduodenal arteries ligated and hepatic artery one-half occluded* after 0 days; completely occluded after 15 days; arteries at porta excised after 29 days	Appeared healthy; killed after 45 days	Slight round cell infiltration of liver; normal distribution of carbon in Kupffer cells	
4	Right gastric and gastroduodenal arteries with partial occlusion of hepatic artery at 0 days; hepatic artery completely occluded after 9 days	Seemed normal; killed after 21 days	Postmortem injection of aorta with barium showed blood entering liver through phrenic arteries; slight round cell infiltration	Injection with 12.5% india ink (30 cc.) at 41 and 43 days intravenously
5	Hepatic artery ligated at 0 days; arteries at porta excised after 13 days; phrenic arteries ligated after 22 days	Appeared healthy; killed after 35 days	Hepatic cells foamy with high grade vacuolization; gallbladder much shrunken; acute cholecystitis; much submucosal infiltration of polymorphonuclears and connective tissue proliferation in the wall	Circulation time, 75 sec.
6	Hepatic artery ligated at 0 days; arteries at porta excised after 7 days	Apparently normal; killed after 29 days	Gallbladder normal; liver cells very foamy	Circulation time, 85 sec.
7	Same as on dog 6; left diaphragm vessels ligated after 17 days	Normal behavior; killed after 29 days	Much cholecystitis with polymorphonuclear and connective tissue proliferation	Circulation time, 90 sec.
8	Gastroduodenal and right gastric arteries ligated at 0 days; dummy abdominal operations after 11, 21 and 30 days	Normal behavior	Liver cells very foamy	Control experiment

* Occlusion with the clamp described by Goldblatt, Lynch, Hanzal and Summerville.

In three dogs at a further sitting the peritoneal attachments of the liver to the diaphragm, esophagus, stomach and posterior abdominal wall were removed, and the adventitia was removed from the hepatic veins with sharp dissection. In two of the latter three dogs, both phrenic arteries were also ligated, while in the third the left phrenic artery only was ligated. This operation was tedious and was best carried out through a long midline anterior incision.

The results are shown in table 2. There was no fatality in this series. The dogs were in good condition after operation, gained weight and were killed after from twelve to ninety-two days. The chief abnormality noted at necropsy was a shrunken gallbladder, the site of an acute cholecystitis with inflammatory changes extending throughout the wall. The liver showed no abnormalities. In some cases the cells were slightly fatty, in others there was slight cellular infiltration, and in yet others foamy cells, but we have frequently seen these changes in dogs supposed to be normal.

The arterial circulation time was determined. After surgical exposure the portal vein was ligated, and 10 cc. of 15 per cent solution of sodium ferrocyanide ($Na_4Fe(CN)_6.12\ H_2O$) was rapidly injected into an exposed femoral vein, the beginning of the injection being noted with a stop watch. An incision was then made in the liver, and the blood oozing from the cut surface was collected on gauze saturated with 10 per cent solution of nitric acid and 10 per cent solution of ferric chloride. The time of first appearance of the prussian blue color was noted. In three normal dogs the time of appearance was twenty, twenty-one and twenty-eight seconds. In three dogs with subtotal arterial removal the time of appearance was seventy-five, eighty-five and ninety seconds. In two dogs with subtotal arterial removal the oxygen content (in volumes per cent) of the portal vein was 16.10 and 10.88, and that of the hepatic vein, 12.89 and 4.82, respectively.

EXPERIMENT 3.—*Acute ligation of the common hepatic artery in rats.*

This structure was ligated just after its origin from the celiac axis in seventeen albino rats. Eleven died within seventy-two hours (65 per cent); five died before the twelfth day, and one died on the twenty-eighth day. The liver of the rats which died on or before the twelfth day usually showed large areas of coagulation necrosis and infarction; the necrotic areas frequently involved more than half a lobe. It was frequently found that areas of the liver appeared normal while others were extensively necrotic.

COMMENT

Within recent years three opinions have been given regarding the necessity of arterial blood for survival of the liver. Cameron and Mayes (1930) stated that "the liver cells die when they are deprived of arterial blood." According to Loeffler (1936), "it can be concluded without objection from the results of my experiments on rats and rabbits that the liver can survive on portal vein blood alone." Livierato, Vagliano and Dervenaga, who removed the hepatic artery in stages (1935), stated that "the complete privation of arterial blood does not influence the life of the animal."

In the present experiments it was found that acute ligation of the principal vessels at the porta hepatis was always fatal. The outcome seemed to be directly related to liver autolysis, the lethal effects of which have been explained satisfactorily by Ellis and Dragstedt[19] and by Andrews and Hrdina[20] as due to infection by anaerobic bacteria of the Clostridium Welchii group normally present in the livers of grown dogs. A consideration of a single animal (table 1, no. 6) which died twelve days after operation from a ruptured gallbladder leads one to suppose that this operation may not be invariably fatal as would appear from the experiments of Haberer and of Whipple and Sperry.

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[19] Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, Arch. Surg. **20**:8 (Jan.) 1930.

[20] Andrews, E., and Hrdina, L.: Surg., Gynec. & Obst. **52**:61, 1931

In contrast with sudden ligation of the principal arterial supply are the experiments in which ligation in multiple stages was done, which was well borne by the animals. The greatest changes developed in the gallbladder, in which acute cholecystitis occurred frequently. Apparently if the arterial circulation is gradually reduced, death from anaerobic bacteria does not occur and the liver becomes accommodated to deprivation of most of its arterial blood.

It seems impossible to remove arterial blood completely from the liver. In addition to the hepatic and phrenic arteries and fine vessels in the lesser omentum and from the esophagus which may be removed in stages, there are fine arterioles (vasa vasorum) in the hepatic and portal veins and the common bile duct, readily apparent on injection of the aorta with barium sulfate, which are more difficult of removal. Further, adhesions form to the new operative sites necessary in multiple stage operations. The amount of arterial blood entering the liver after removal of the hepatic and phrenic supply must, however, be small.

The oxygen determinations on the blood of the portal and hepatic veins clearly show that further reduction of portal blood occurs in the liver.

CONCLUSIONS

In dogs, ligation of the hepatic artery and its largest collaterals, the gastroduodenal and the right gastric artery, in one stage was fatal. Preliminary ligation of the hepatic artery proximal to this point of anastomosis was never fatal and permitted subsequent ligation of collaterals, including the phrenic and cystic arteries.

After subtotal arterial removal in stages, no histologic or physiologic abnormalities were detected in the liver. Acute cholecystitis frequently developed.

The liver is able to utilize oxygen from the blood of the portal vein.

Prof. E. S. Guzman Barron made the determinations of blood oxygen.

LYMPHOID HYPERPLASIA OF THE APPENDIX

WITH A NOTE ON ITS ROLE IN ACUTE APPENDICITIS

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In the routine examination of appendixes removed at operation we were impressed by the unusual richness of the lymphoid tissue as the prominent histologic feature in a group of cases presenting the clinical syndrome of a mildly acute, subacute or recurrent appendicitis. Our studies led us to believe that hyperplasia of lymphoid tissue, either focally or diffusely, may cause sufficient obstruction in the narrow-lumened appendix to produce symptoms simulating appendicitis. Furthermore, in reviewing a series of cases of pathologically early acute appendicitis, we felt that here, too, the hyperplasia of the lymphoid tissue might be a factor of prime etiologic importance.

Lymphoid hyperplasia of the appendix has been described by Wätzgold,[1] Klemm,[2] Miloslavich,[3] Stout,[4] Moschcowitz,[5] Barss,[6] Symmers and Greenberg[7] and Smith.[8] Most of these investigators considered it a phase of status lymphaticus. Smith thought that it constituted a definite clinical entity.

Since all gradations in the amount and activity of the lymphoid tissue in the appendix may be present both in the same person and in different

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From the Laboratory of the Jewish Hospital.

This work was aided by a gift in memory of Mrs. Carrie Scott Johnson.

[1] Wätzgold: Beitrag zur pathologischen Anatomie des Wurmfortsatzes unter besonderer Berücksichtigung der Ausheilungserscheinungen der Appendicitis acuta, Beitr. z. path. Anat. u. z. allg. Path. **42**:260, 1907.

[2] Klemm, P.: Ueber die Erkrankung des lymphatischen Gewebes und ihr Verhältnis zur Appendicitis, Deutsche Ztschr. f. Chir. **81**:427, 1906.

[3] Miloslavich, E.: Zur Pathogenese der Appendizitis, Wien. klin. Wchnschr. **25**:442, 1912.

[4] Stout, A. P.: Isolated Lymphoid Hyperplasia in the Cecum and Appendix of Children, Am. J. Dis. Child. **34**:797 (Nov.) 1927.

[5] Moschcowitz, E.: The Pathological Diagnosis of Diseases of the Appendix Based on the Study of 1,500 Specimens, Ann. Surg. **63**:697, 1916.

[6] Barss, H. deB.: Lymphatic Disease in Children Simulating Appendicitis, Am. J. Dis. Child. **15**:421 (June) 1918.

[7] Symmers, D., and Greenberg, M.: Clinical Significance of Lymphoid Hyperplasia of the Appendix, J. A. M. A. **72**:468 (Feb. 15) 1919.

[8] Smith, T. A.: *Lymphoid Hyperplasia of the Appendix in Children*, Ann. Surg. **79**:871, 1924.

persons, it was necessary to establish some arbitrary standard by which we could select our cases of lymphoid hyperplasia. We included in our study only those appendixes with one half or more of the entire wall composed of lymphoid tissue. In addition, the follicles exhibited definite signs of hyperactivity, as shown by an increase in the size of the germinal centers and the presence of mitoses, phagocytosis and dilatation of the lymphatics in the muscular and serosal coats.

The appendixes were fresh when brought to the laboratory. Cross-sections were made usually proximal to the middle and near the tip. The site of a single section, as far as could be ascertained, was distal to the middle. When tissue was available, more sections were cut. The tissue was fixed in a solution of formaldehyde.

In the years 1926 to 1933 inclusive, there were approximately fourteen hundred appendectomies performed at the Jewish Hospital. We have examined the records of all these cases and have uncovered fifty-one in which a definite diagnosis of lymphoid hyperplasia of the appendix could be made. No cases in which the diagnosis was doubtful are included in our series.

The data on these cases are presented in the following outline:

I. Incidence

Sex: Male............15 Female............36

Age:			
1 to 5	2	21 to 25	11
6 to 10	6	26 to 30	2
11 to 15	14	31 to 35	1
16 to 20	15		

Average age: 17 Lowest age: 3 Highest age: 35

II. History

Duration of attack (on admission):

Over 3 days	23
1 to 3 days	9
Less than 24 hours	19

	Present	Absent	Not Recorded
Nausea	35	13	3
Vomiting	23	25	3
Constipation	11	29	11
Previous attacks	28	19	4
Symptoms of infection of the upper respiratory tract	13	17	21

III. Physical Findings

	Marked	Moderate	Slight	Absent	Not Recorded
Tenderness	10	27	13	1	0
Rigidity	2	7	21	21	0
Rebound tenderness	1	0	13	24	13
Meltzer's sign	0	8	10	20	13

Rectal temperature (on admission):

Below 100 F.	27
100 to 100.8 F.	18
101 to 101.8 F.	4
102 F. and over	2

Highest temperature: 103.8 F.

Leukocyte count:

4,000 to 6,000	3	12,000 to 14,000	12
6,000 to 8,000	11	14,000 to 16,000	10
8,000 to 10,000	16	16,000 to 19,000	2
10,000 to 12,000	14		

Average count........... 10,350 Maximum count.......... 18,800

Minimum count............ 4,650

The seventeen extra leukocyte counts were those repeated on several patients during their preoperative stay in the hospital.

Differential count: A Schilling differential count was done in eleven cases. In only one case was there a relative increase in the neutrophilic cells. In four cases there was a shift to the left. In none of the cases was there lymphocytosis. The average leukocyte count was 9,800.

IV. Preoperative Diagnosis:

Acute appendicitis	22
Subacute appendicitis	17
Chronic appendicitis	2
Recurrent appendicitis	10

V. Postoperative Course:

In nearly all cases the postoperative course was uneventful. There was infection of the wound in one. One patient died a year later of acute myelogenous leukemia.

To summarize the foregoing data briefly, we are confronted with a picture hardly distinguishable from that of mild appendicitis. The patients, twice as often female as male and most often adolescents or young adults, entered the hospital after having had one or more attacks of pain in the right lower abdominal quadrant. The pain was usually cramplike or dull but sometimes quite sharp and colicky, and in several cases it was of such severity as to make the patient "double up." It lasted anywhere from several hours to several days, and as a general rule the longer its duration, the less its severity. The pain remained localized in this area and never radiated. Sometimes there was a remission and then a recurrence. In most cases there was a history of previous attacks of similar pain. Pain was the only symptom that was always present, and its location immediately centered the attention of the surgeon and frequently that of the patient on the appendix. Nausea was usually present. Vomiting occurred in half the cases at some time during the course of the illness. Constipation was present in about a fourth of the cases. Some mention of signs or symptoms referable to the upper respiratory tract, such as a cold, a sore throat, rhinitis and pharyngitis, was made in about a third of the cases.

On physical examination tenderness of varying degrees, but usually moderate, was always present. Slight rigidity was generally present. Rebound tenderness and a positive Meltzer sign were inconstant. A slight elevation of temperature was often present when the patient was admitted to the hospital. It was noticed that in some of these cases the fever subsided when the patient was put to bed for a day or two. If any figure up to 10,000 is considered as a normal leukocyte count for this age period, we find that in slightly more than half the cases there was a mild leukocytosis. The few Schilling hemograms taken gave inconstant values.

The patients went to operation with a certain or likely diagnosis of acute, subacute or recurrent appendicitis. The appendixes were described grossly as being anywhere from "normal" to "bound down by adhesions." A frequent notation was the presence of congested vessels in the subserosa. The operative report on three cases mentioned enlarged ileocolic lymph nodes.

We have not made any attempt to locate these patients to determine if symptoms persisted postoperatively, but the occasional patient whom we have subsequently encountered has been almost entirely free from a recurrence of symptoms. One complained of some slight pain similar to that experienced before operation but less severe.

It may be of interest to summarize briefly the observations of previous investigators. Barss[6] in 1918 reported a syndrome strongly suggestive of recurrent attacks of appendicitis in seven children, i. e., localized nonradiating pain in the right lower abdominal quadrant lasting from several hours to several days, usually accompanied by nausea but rarely by vomiting. Constipation and headache were frequent symptoms. There was no fever or leukocytosis. The only constant physical sign was localized tenderness. Muscle spasm was absent in most cases. At operation, enlarged mesenteric lymph nodes were usually found. The notable change microscopically was hyperplasia of the lymphoid tissue of the appendix. The author ventured the opinion that this might be one of the manifestations of "status lymphaticus."

Symmers and Greenberg[7] examined several thousand appendixes at the Bellevue Hospital and noticed that lymphoid hyperplasia was the sole pathologic change in 10 per cent. A study of twenty typical cases, ten in males and ten in females, was made. The average age was 17½ years. There was a history of from two to eight attacks of pain lasting several hours or days, referable to the region of the appendix. The temperature, pulse and leukocyte count were usually normal. Constipation, headache and nausea were frequent, and vomiting was rare. The authors attributed this condition to the instability of the lymphatic system generally associated with a mild "status lymphaticus."

Smith[8] reviewed thirty-seven cases occurring in a period of eight years in children under 12½ years in the children's surgical service at the Bellevue Hospital. Twenty-two cases occurred in girls and 15 in boys. All the patients gave a history of colicky pain, often intermittent, starting about the umbilicus and later localizing in the right iliac region. Three fourths gave a history of previous attacks. Two thirds had symptoms of nausea and vomiting. Localized tenderness was present in all, and rigidity of some degree was present in one half. A slight elevation of temperature was frequently noted on the patient's admission, but usually subsided when he was put to bed. The average leukocyte count in twenty-nine cases was 10,700, which the author considered normal for this age period. There were, however, seven cases in which the leukocyte counts ranged between 12,000 and 15,000. All patients had satisfactory postoperative courses. Thirty-one were followed for periods of from three months to six years, and except for two, were entirely free from further abdominal symptoms.

PATHOLOGIC PICTURE

On gross examination of an appendix with lymphoid hyperplasia the usual findings of an acute inflammatory process are absent. The serosa is pale, shiny and smooth, and the wall is moderately thickened. On cross-section the lumen is quite diminished in size and sometimes is almost occluded. Frequently it has a slitted or stellate appearance. The lumen may vary in shape and size in the same appendix. Slight pressure near the cut end pushes out the mucosa and submucosa and demonstrates that these layers occupy more than half the wall. The hyperplastic lymph follicles can be seen in bright daylight as small yellow or pink areas the size of a pinpoint, some of which produce distinct elevations of the mucosa.

Microscopically, the most notable change is the absolute and relative increase in the amount of lymphoid tissue, evidenced chiefly by the large lymph follicles (fig. 1). The lymphoid tissue frequently occupies as much as three fourths of the wall. The individual follicles are considerably enlarged. Their normal spherical shape tends to become ovoid, the long diameters being arranged radially around the lumen. The contour of the latter is largely determined by the size, shape and arrangement of these follicles. Occasionally two adjacent follicles have so elevated their overlying mucous membrane as to leave a deep cryptlike depression between the two swellings (fig. 2). The same appendix may, in different sections, show hyperplastic follicles, normal follicles or both. Of course one must always bear in mind that many follicles are sectioned eccentrically and hence give the appearance of normal size.

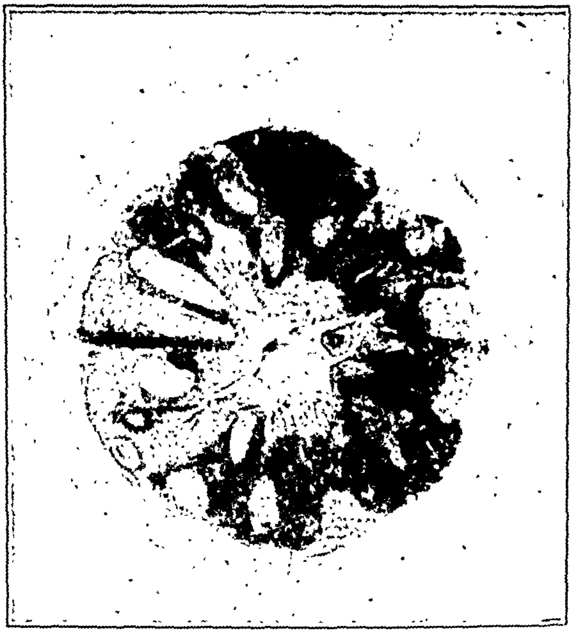

Fig. 1.—Cross-section of an appendix showing hyperplasia of the lymphoid tissue, which occupies well over half the wall. The hyperplastic follicles consist chiefly of germinal centers. Hematoxylin and eosin stain; × 7.

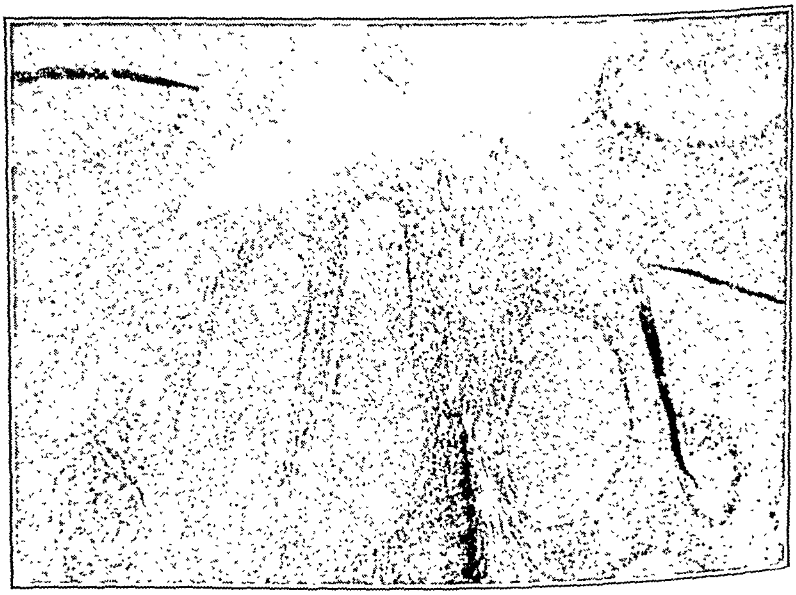

Fig. 2.—Crypt formation between hyperplastic lymph follicles. Hematoxylin and eosin stain; × 25.

The lymph follicles are in a state of hyperactivity. Each follicle contains a large light central area, the germinal center, surrounded by a thinner zone of denser hue. The germinal center (fig. 3) is composed of large, loosely arranged, somewhat irregular cells. Most of these are reticulum cells, the nuclei of which stain lightly and contain small amounts of finely stippled or strandlike chromatin, a dense, almost black, irregular nucleolus and a fine nuclear membrane. The remainder of the cells are chiefly large and medium-sized lymphocytes. Occasionally one sees a cell which seems to be transitional from the reticulum cell to the large lymphocyte. Mitoses are fairly common. Tissue eosinophils and plasma cells are rare. Other changes in the germinal centers include rare tissue macrophages with phagocytosed nuclear material and some pyknotic nuclear material. This phagocytosis is probably not above physiologic limits. Polymorphonuclear cells are almost completely absent. The outer zone of the follicles consists of densely packed, more uniform and medium-sized lymphocytes. The changes present are more indicative of an active physiologic process than of a toxic or destructive lesion. No changes are present which cannot be duplicated in normal secondary lymph nodules at one time or another. The differences from the normal lymph follicle are quantitative rather than qualitative.

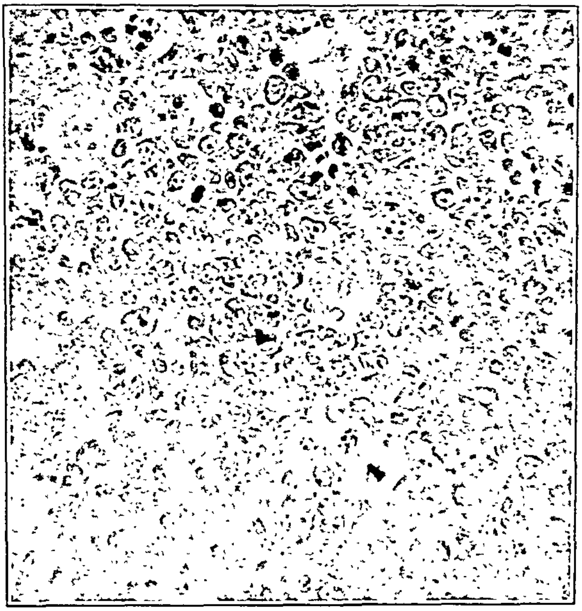

Fig. 3.—Section through the germinal center of a hyperplastic lymph follicle, showing several mitotic figures and phagocytic cells containing fragments of ingested nuclear débris. Hematoxylin and eosin stain; × 400.

We have measured typical examples of hyperplastic lymph follicles and have found many to measure well over 1.5 mm. in diameter. The largest follicle measured 2.25 by 1.75 mm. However, they usually averaged slightly more than 1 mm. in their longer diameters and slightly less than 1 mm. in their shorter diameters.

COMMENT

Liebeck[9] has shown that the lymphoid follicles occupy about 30 per cent of the mucosal surface of the appendix. The variations lie between 8.2 and 52.8 per cent. Changes with age in the amount of lymphoid tissue do not correspond entirely with changes in the size of the appendix as a whole. The appendix grows only slightly from birth to adolescence. From puberty to the age of 35 years its size is usually constant.[10] The lymphoid tissue, however, increases at a slightly greater rate than the appendix as a whole, so that the greatest amount of lymphoid tissue, both relatively and absolutely, is present between 17 and 35 years.[11] In this respect, the lymphoid tissue of the appendix differs from that of the remainder of the body. Whitney[12] has shown that the lymphoid tissue in general reaches its relative maximum during the ages of 2 to 5. After this period there is a gradual decrease until adolescence, when there is a sudden decrease in the relative amount of lymphoid tissue. The total amount of lymphoid tissue by weight, however, shows a gradual increase until adolescence, when it reaches a constant level, which is maintained until about the twenty-fifth year of life.

The peak of the number of follicles in the appendix is present between 10 and 20 years.[13] At this stage the follicles vary between 0.8 and 1 mm. in diameter. The number of follicles in the appendix is estimated by Berry and Lack[14] at 200 and by Keeley and Hundin[15] at from 300 to 400. The lymphoid tissue increases in density toward the tip.[16]

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[9] Liebeck, cited by Berry and Lack.[14]

[10] Nowicki, W.: Anatomische Untersuchungen über Appendix und Appendizitis, Virchows Arch. f. path. Anat. **195**:177, 1909.

[11] Shiota, H.: Ueber das Verhalten des Wurmfortsatzes bei Lymphatismus, Wien. klin. Wchnschr. **22**:1101, 1909.

[12] Whitney, C.: Hyperplasia of Lymphoid Tissue and Lymphocytosis, Medicine **7**:1, 1928.

[13] Nagoya, C.: Ueber die Drüsen und die Follikel des Wurmfortsatzes, Frankfurt. Ztschr. f. Path. **14**:106, 1914.

[14] Berry, R. J. A., and Lack, L. A. H.: The Vermiform Appendix of Man and the Structural Changes Therein Coincident with Age, J. Anat. & Physiol. **40**:247, 1905-1906.

[15] Keeley and Hundin, cited by Berry and Lack.[14]

[16] Wätzgold.[1] Berry and Lack.[14]

Several factors seem to stimulate the lymphoid tissue. That most frequently emphasized is infection, against which the tissue constitutes a defensive mechanism for the body.[17] Responses to physical and chemical irritations have been noted.[12] Many observations tend to show that lymphoid tissue, particularly that along the alimentary canal, is greatly concerned with the metabolism of fat[18] and during this function may undergo hyperplastic changes. Bunting[19] expressed the belief that there is a variation in the resistance of the lymphoid tissue, depending on age and sex. He found that the lymphatic system is most susceptible to injury in the immediate postpuberty years, with the male less resistant than the female.

The most characteristic response of lymphoid tissue to any agent is hyperplasia. This response may result not only from toxic and physical agents but from physiologic activity. Progressive and retrogressive changes in activity are constantly occurring during the regular stresses and strains of physiologic activity. Frequent swelling of the lymph glands of an insidious nature come and go without an obvious etiologic agent. Although the various lymphoid organs and lymph follicles tend to be interdependent and interresponsive, hyperplastic changes may occur at a site entirely remote from the original focus of stimulation. Thus it is entirely possible for focal hyperplasia to occur without similar involvement elsewhere.[20] The lymphatic system as a whole is very labile, unpredictable and variable in its systemic and local response. Given a certain etiologic agent, either pathologic or physiologic, and the response may be a generalized lymphatic reaction or one confined locally or remotely.

The vermiform appendix is largely a lymphoid organ. Hence its lymphoid response is subject to the same variations and etiologic factors as lymphoid tissue elsewhere. The association of mild appendical symptoms with acute infections of the upper respiratory tract has been frequently noted.[21] Along with, or independent of, other lymphoid

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17. Beitzke, H.: Ueber den lymphatischen Rackenring und seine Rolle als Eintrittspforte von Infektionen, Wien. klin. Wchnschr. **39**:1473, 1926. Whitney.[12]

18. (*a*) Dudgeon, L. S., and Mitchiner, P. H.: Bacteriological and Pathological Examination of the Vermiform Appendix in the First Thirty Hours of Acute Appendicitis, Brit. J. Surg. **11**:676, 1924. (*b*) Lefholz, R.: The Effect of Diets Varying in Caloric Value and in the Relative Amounts of Fat, Sugar, and Protein upon the Growth of Lymphoid Tissue in Kittens, Am. J. Anat. **32**:1, 1923. (*c*) Settles, E. L.: The Effect of High Fat Diet upon the Growth of Lymphoid Tissue, Anat. Rec. **20**:61, 1921.

19. Bunting, C. H.: Variations in Lymphoid Resistance, Tr. A. Am. Physicians **41**:30, 1926.

20. Stout.[4] Nagoya.[13]

21. Brennemann, J.: "The Abdominal Pain in Throat Infection in Children" and Appendicitis, J. A. M. A. **89**:2183 (Dec. 24) 1927. Lowenstein, P.: Respiratory Diseases That Mimic Appendicitis, J. Missouri M. A. **29**:563, 1932.

organs, the follicles of the appendix may undergo hyperplastic changes, either all or only a few of the follicles being involved. Follicles may be involved at the tip or at the base; a group may become hyperplastic on one side of the lumen or on the other. After the inciting agent is removed or successfully overcome, the follicles may return to normal. These changes are constantly at work in the appendix as in other lymphoid structures. We feel that clinical symptoms result from the response of the lymphoid tissue in a narrow-lumened organ to these variable stimuli. This usually occurs during the period in life when the lymphoid tissue is normally at its richest.

Our choice of fifty-one appendixes may be considered arbitrary. It so happens that in these the process was shown to the best advantage in the chance sections obtained. It is likely that many other appendixes showed similar undiscovered processes at the time they were removed. In fact, it would be logical to assume that most appendixes undergo some lymphoid hyperplasia at one time or another, it being physiologic and asymptomatic in a large majority.

The relationship between lymphoid hyperplasia of the appendix and status lymphaticus that previous workers have stressed we think unwarranted. Hart[22] wrote in 1923:

> The doctrine of Status Thymico-Lymphaticus has shared the fate of so many other doctrines. Only reluctantly adopted at first by medical men, it has become more and more the prey of uncritical application and exaggeration and at last a great receptacle for everything (zu einem grossen Sammelbecken geworden) into which every conceivable morphological and functional appearance is thrust, so practically the whole field of pathology is covered by the Status Thymico-Lymphaticus. It is, to use an expression of Pfaundler's, denatured into a "pandiathesis."

More recently, the report of a comprehensive survey by the Status Lymphaticus Committee[23] ended with the sentence:

> In the opinion of the committee the facts elicited in the present inquiry were in harmony with those of Hammer (1926 and 1929) and Greenwood and Woods (1927) in affording no evidence that so-called "status thymico-lymphaticus" has any existence as a pathological entity.

The mechanism of pain and nausea in our cases of lymphoid hyperplasia probably is similar to that in cases of acute appendicitis. Morley[24] expressed the belief that appendical pain has two components. The initial pain varies in intensity but is usually dull and spasmodic and often accompanied by nausea. Tenderness is not marked, and rigidity is usually absent. This pain is due to increased tension on the muscular wall. Hertz[25] and Ryle[26] have experimentally shown that increased tension on the muscular wall of a hollow viscus results in similar pain. Obstruction to the lumen is a factor, since it also increases the muscular tension. The secondary pain occurs later and is much sharper and better localized; more tenderness is present, and there is definite rigidity. This pain is due to extension of the process to the peritoneum.

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[22] Hart, cited by Greenwood, M., and Woods, H. M.: "Status Thymico-Lymphaticus" Considered in the Light of Recent Work on the Thymus, J. Hyg. **26**:305, 1927.

[23] Young, M., and Turnball, H. M.: An Analysis of the Data Collected by the Status Lymphaticus Committee, J. Path. & Bact. **34**:213, 1931.

[24] Morley, J.: Abdominal Pain as Exemplified in Acute Appendicitis, Brit. M. J. **1**:887 (May 26) 1928.

It is the initial type of pain which we recognize as occurring in lymphoid hyperplasia. The secondary type is notably absent. The swelling of the lymph follicles might produce the same tendency to stretch the muscular wall as an acute inflammatory swelling of the mucosa and submucosa. The lumen of the appendix is normally small, and the wall is quite rigid. In many cases hyperplasia of several follicles would be sufficient to occlude the lumen enough to result in stasis, causing forceful propulsive muscular contractions behind the occlusion. The occlusion may also be assisted by the presence of inspissated feces or other material. It is not necessary for the entire appendix to become involved in this process. One small occlusive process would be sufficient. In this respect the appendix differs from, for instance, the ileum. In the latter organ no degree of lymphoid hyperplasia of Peyer's patches would be productive of a similar occlusion or even stretching of the muscular wall. Smith[8] mentioned that at least some of the pain from appendical lymphoid hyperplasia is due to stretching of the serosa resulting from swelling of the follicles.

The occasional presence of leukocytosis needs a few words of comment. In the age group considered here the variability of leukocyte counts is sufficient to make the establishment of a definite maximum level of normal difficult. The few counts that are distinctly elevated may be due to the presence of some mild unrecognized intercurrent infection. It is possible, of course, that this intercurrent infection may also invite, in addition to the usual defensive mechanisms of the body, the hyperplastic response of lymphoid tissue. Fever falls in the same category. Many patients on first entering the hospital show an initial unexplained slight elevation of temperature.

It is also conceivable that many of these instances of lymphoid hyperplasia, especially those in which leukocytosis or fever is present, may be aborted cases of very mild acute appendicitis in which the minute lesion was not found. This concept takes on definite possibilities, from the evidence we have gathered, that lymphoid hyperplasia may be an important etiologic factor in the production of acute appendicitis.

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[25] Hertz, A. F.: The Goulstonian Lectures on the Sensibility of the Alimentary Canal, London, H. Frowde, 1911.

[26] Ryle, I. A.: Visceral Pain and Referred Pain, Lancet 1:895 (May 1) 1926.

The early years of the present century were productive of two main theories of origin of acute appendicitis. Kretz[27] was an early advocate of the hematogenous (from the tonsils) origin of acute appendicitis, and his supporters were many.[28] Aschoff[29] formulated the enterogenous theory of origin, in which he described the earliest stages of acute appendicitis originating in the depths of the mucous crypts and spreading through the walls from this original focus. The intervening years have seen numerous battles between these two schools, but more recently the evidence on the side of Aschoff has become so great that most observers at present favor the enterogenous theory.[30] We, too, adhere to Aschoff's concept so far as the original site and spread of the infection are concerned. But we venture to go back one step and state that hyperplasia of the lymph follicles may be responsible for the deepening of the crypts and for the closing off of their free connection with the main lumen, thereby promoting stasis in the depths of the crypts. A comparable process occurs in acute tonsillitis. This concept of the origin of acute appendicitis also conforms with repeated and well substantiated observations that acute appendicitis has some relationship to generalized infections,[31] observations on which much of the hematogenous theory

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[27] Kretz, R.: Studies on the Etiology of Appendicitis, Internat. Clin. **3**:285, 1908.

[28] Anderson, H. B.: Appendicitis as a Sequela of Tonsillitis, Am. J. M. Sc. **150**:541, 1915. Chase, C.: The Etiology of Appendicitis, Am. J. Obst. **73**:444, 1916. McCoy, F. C.: The Rôle of the Tonsil in the Production of Appendicitis, Lancet-Clinic **116**:49, 1916. Poynton, J., and Paine, A.: A Further Contribution to the Study of the Etiology of Appendicitis as a Result of Blood Infection, Lancet **2**:439, 1912. Wilkie, P. D.: The Etiology of Acute Appendicular Disease, Canad. M. A. J. **22**:314, 1930.

[29] Aschoff, L.: Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908.

[30] Böhne, Carl: Untersuchungen zur Pathogenese der Wurmfortsatzentzündung, Arch. f. klin. Chir. **171**:692, 1932. Kühnel, P.: Some Examinations of the Local Eosinophilia in the Vermiform Appendix, Acta chir. Scandinav. **53**:476, 1920-1921. McMeans, J. W.: Experimental Appendicitis, Arch. Int. Med. **19**:709 (May) 1917. Riff, A.: Contribution à l'étiologie de l'appendicite, Presse méd. **27**:521, 1919. Steinberg, B.: Degenerative Lesions of the Appendix, Am. J. Clin. Path. **1**:339, 1931. Warren, S.: The Etiology of Acute Appendicitis, Am. J. Path. **1**:241, 1925. Wätzgold.[1] Moschcowitz.[5]

[31] Armstrong, A. W.: The Causes of Appendicitis, New York M. J. **87**:66, 1908. Evans, J. S.: Epidemiology of Acute Appendicitis in Relation to Acute Nasal and Tonsillar Infections, Wisconsin M. J. **17**:91, 1918. Herzberg, M.: Giant Cells in the Lymphoid Tissue of the Appendix in the Prodromal Stage of

(Footnote continued on next page)

of the origin of acute appendicitis rests. This relationship may well be through the general lymphatic system, the appendical lymphoid tissue playing a rôle in this by becoming hyperplastic. Thus it is possible to reconcile the enterogenous and hematogenous theories through the intermediacy of the lymphoid tissue of the appendix.

Statistics show that acute appendicitis occurs most frequently in the postpuberty years and early adulthood.[32] A glance at our figures shows that our cases of lymphoid hyperplasia fall into the same age groups. This is the period of life when the lymphoid tissue is normally richest. These facts seem significant.

The infrequency of appendicitis in such countries as China, India, Arabia and Africa, where careful observations on the native populations show them to be practically immune to this disease, has never been adequately explained. Most investigators agree that the most important factor is diet.[33] From the data we have been able to obtain the chief difference in diet is a lower consumption of protein and fat in these countries. In the past the protein factor was held responsible, although its mode of action was not known. If we consider the fat factor, however, in the light of the experiments of Settles[18c] and Lefholz,[18b] who have shown that prolonged fat diets produce hyperplasia of lymphoid tissue, we have here a possible linking of diet and acute appendicitis through the lymphatic system.

Measles: Report of Isolated Case, J. A. M. A. **98**:139 (Jan. 9) 1932. Hunt, W. M.: The Relation Between Tonsillitis and Appendicitis, Am. J. Surg. **6**:761, 1929. Watson-Williams, P.: Nasal Sinus Infections as a Causal Factor in Appendicitis, Practitioner **106**:229, 1921.

[32] Bancroft, F. W.: Acute Appendicitis: A Review of Five Hundred and Eighty-Four Consecutive Cases, J. A. M. A. **75**:1635 (Dec. 11) 1920. Beekman, F.; Smith, M. K., and Everingham, S.: Acute Appendicitis: An Analysis of Five Hundred Cases, Am. J. M. Sc. **154**:490, 1917. Flint, E. R.: Acute Appendicitis: A Study of Three Hundred and Seventy Cases, Practitioner **104**:352, 1920. Keyes, E. L.: Death from Appendicitis, Ann. Surg. **99**:47, 1934. Maylard, A. E.: Sex and Age Incidence in Appendicitis, Brit. J. Surg. **8**:189, 1920.

[33] Crichlow, N.: A Case of Appendicitis in a Native of the Solomon Islands, Western Pacific, J. Trop. Med. **23**:22, 1920. Gibson, R. M.: The Incidence of Appendicitis in Chinese, China M. J. **40**:43, 1926. Mantle, A.: The Cause of Appendicitis, Brit. M. J. **1**:399, 1911. Reyes, C.: Appendicitis Among Filipinos, J. Philippine Islands M. A. **5**:75, 1925. Shaheen, H. I.: The Cause of Appendicitis, Brit. M. J. **1**:165, 1911. Waller, H. W. L.: A Case of Acute Appendicitis in a Native of Africa, J. Trop. Med. **22**:1, 1919. Weischer, P.: Ueber Perityphlitis bei Chinesen, Zentralbl. f. Chir. **50**:875, 1923. Williams, O. T.: Microchemical Changes Occurring in Appendicitis, with a Note on the Incidence of the Disease in Various Countries, Biochem. J. **3**:391, 1908.

CONCLUSIONS

Lymphoid hyperplasia of the appendix was found in fifty-one of a group of fourteen thousand appendixes.

The clinical symptoms presented simulated those of mild acute appendicitis.

The clinical picture is explained on the basis of an obstruction by hyperplasia of lymphoid follicles in a narrow-lumened organ, occurring during a period of life when the lymphoid tissue is normally richest.

A theory is presented indicating the possible etiologic relationship between lymphoid hyperplasia and acute appendicitis.

THE ADRENAL CORTEX

A CYTOLOGIC STUDY OF NORMAL AND OF PATHOLOGIC TISSUE

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The adrenal gland was first described by Eustachius [1] in 1564 and the adrenal medulla, by Bartholin [2] in 1666. The adrenal gland of man, as such has been the object of considerable study in the past. These studies, however, have been directed primarily to the chemical nature of the cells of both the cortex and the medulla. Various workers who have dealt with pathologic adrenal tissue have stressed the cell unit rather than the individual components of the cell.

Study of malignant cells indicates that there is an absence of normal differentiation, specific function and intercellular organization. It is to these characteristics that Hansemann [3] applied the term "anaplasia" in his early publications. Anaplasia is associated with changes in the morphologic characteristics of the cells; such changes occur to a lesser degree in association with reparative regenerative hyperplasia and in benign cells. Because of morphologic gradations, the approach to an early diagnosis of a malignant process must be made by careful study of the individual cell and its individual parts.

For more than fifty years there has been a constant attempt to recognize cytologic differences which might aid in the differential diagnosis of malignant conditions. Stenius [4] in 1925 observed a relative increase in the size of the nucleoli of malignant cells in urinary sediment, and

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Abridgment of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

[1] Eustachius, cited by Stöhr, P., and Lewis, F. T.: A Textbook of Histology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1913, p. 404.

[2] Bartholin, cited by Stöhr, P., and Lewis, F. T.: A Textbook of Histology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1913, p. 404.

[3] Hansemann, David: Ueber asymmetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung, Virchows Arch. f. path. Anat. **119**:299-326 (Feb. 4) 1890.

[4] Stenius, Fjalar: Zur Bewertung des epithelialen Harnsedimentes für die Diagnose der Blasengeschwülste. Acta chir. Scandinav. **58**:240-255, 1925.

studies conducted by Aichel,[5] Hertwig,[6] Heiberg[7] and others attempted to establish such criteria for the diagnosis of malignant processes. They studied the relationship between nuclei and cytoplasm and stated that the low nucleoprotoplasmic ratio, which at first was thought to be characteristic of malignant cells, was also present in embryonic cells and that such cells merely represent rapid growth and cell division.

Many years ago MacCarty[8] observed a marked difference in the relative size of the nuclei and nucleoli of benign as compared to malignant cells. In 1924 he published his first articles dealing specifically with this phase of the subject, although his earlier studies had suggested a difference in the size of the nucleoli in regenerative and in malignant cells. Since that time studies have been made on tissue from the breast, large intestine, lymph nodes, uterus and stomach by MacCarty and his colleagues, Haumeder and Berkson,[9] and by McCormack[10] and Naidu.[11] Such a comprehensive cytologic study has not been conducted heretofore on the adrenal gland. It is a well known fact that tumors of the adrenal gland are an uncommon finding, both clinically and pathologically. However, a sufficient number of these tumors have been encountered at the Mayo Clinic so that such a study could be carried out. It is the purpose of this paper, therefore, to present the data for both normal and pathologic adrenal cortex.

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[5] Aichel, cited by Sokoloff, Boris: The Nucleo-Cytoplasmic Ratio and Cancer, J. Cancer Research **7**:395-415 (Oct.) 1922.

[6] Hertwig, R.: Ueber Korrelation von Zell- und Kerngrösse und ihre Bedeutung für die geschlechtliche Differenzierung und die Teilung der Zelle, Biol. Centralbl. **23**:49 and 108, 1903.

[7] Heiberg, K. A.: Studien über Haut-Epithel-Atypie bei Krebs- und Granulationsgewebe und die diagnostische Verwendung der Kerngrösse, Virchows Arch. f. path. Anat. **234**:469-480, 1921.

[8] MacCarty, W. C.: Studies in the Etiology of Cancer: IV. Notes on the Regularity and Similarity of Cancer-Cells, in Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, 1914, vol. 6, pp. 600-602; A Biological Conception of Neoplasia: Its Terminology and Clinical Significance, Am. J. M. Sc. **157**:657-674 (May) 1919; The Cytologic Diagnosis of Neoplasms, J. A. M. A. **81**:519-522 (Aug. 18) 1923; The Early Diagnosis of Cancer, Arch. Clin. Cancer Research **1**:11-20 (Jan.) 1925.

[9] MacCarty, W. C.; Haumeder, Eva, and Berkson, Joseph: A Differential Characteristic of Malignant Cells: Preliminary Report, Proc. Staff Meet., Mayo Clin. **8**:38-45 (Jan. 18) 1933. MacCarty, W. C., and Haumeder, Eva: Has the Cancer Cell Any Differential Characteristics? Am. J. Cancer **20**:403-407 (Feb.) 1934.

[10] McCormack, C. J.: Biometric Studies of Endometrial Cells, Proc. Staff Meet., Mayo Clin. **10**:24-29 (Jan. 9) 1935.

[11] Naidu, V. R.: The Value of Enlarged Nucleoli in the Diagnosis of Malignancy, Proc. Staff Meet., Mayo Clin. **10**:356-362 (June 5) 1935.

METHOD OF STUDY AND MATERIAL USED

Tissue from normal and renal cortices that were removed at necropsy was placed in a solution of formaldehyde. Frozen sections were made after twenty-four hours and stained with hematoxylin. In unfixed specimens of tissue, tracings of the cells were made within a few minutes after removal of the tissue from the living body in order that the cells would not have been altered. With an oil immersion lens and a Spencer microscope (objective, 1.8 mm.; numerical aperture, 1.25; length of tube, 150 mm.; ocular, 10×), the nuclei and the nucleoli of 20 cells from different parts of each section were projected by means of a camera lucida on paper and then were traced. The tracings of the nuclei and nucleoli were measured directly by a planimeter to obtain their areas. The tracings of nucleoli were necessarily further enlarged to obtain measurable areas; this was done by means of a camera lucida and a Spencer microscope (objection, 48 mm.; length of tube, 250 mm.; ocular, 1×). The areas of the nuclei and nucleoli were then corrected to allow for the foregoing magnifications as well as for the planimeter constant. The final true areas of the nuclei and nucleoli were expressed in square microns. Throughout this work care was taken to keep the length of the tube constant, frequent checks being made so that the areas of nuclei and nucleoli from comparable sections were recorded.

The specimens of pathologic tissue were removed at operation. This tissue was studied in essentially the same manner as the normal tissue. The results obtained should be considered only after the embryology, anatomy, histology and pathology of the adrenal cortex are understood. I shall attempt to discuss them briefly.

NORMAL ADRENAL CORTEX

Embryology and Anatomy.—The adrenal gland, of course, has a double origin, but as I am dealing with the cortex I shall discuss only that portion of the gland.

The anlage of the cortex is first noticed in the embryo of 6 mm., wherein a bud projects from the peritoneal mesothelium near the root.[12] In the embryo of 9 mm. these cells have migrated to their positions above each kidney. A differentiation into the mature type of gland does not occur until the end of the third year.[13] At the end of the third month, and in the first half of the fourth month, the gland is larger than its contiguous kidney. At the sixth month it has decreased to one-half, and at birth to one-third, the size of the kidney; in the adult the ratio of the size of the adrenal gland to the kidney is 1:28.[14] The weight of the gland varies from 6 to 7 Gm., the left one being slightly larger that the right. The gland lies above the kidney and has the gross appearance of a cocked hat. Its surface is slightly yellow, and the gland seems to be rather densely adherent to the surrounding structures. Frequently the gland is adjacent to the upper pole of the kidney, the whole having the appearance of being a single structure until close examination reveals a definite difference in tissue. Accessory adrenal tissue is a relatively common anatomic finding, and that found in the broad ligament of the female has been given the name "Marchand's adrenal." Accessory adrenal tissue has been reported in association with every tissue or structure below the diaphragm; usually only cortical tissue is found. As many as 50 per cent of new-born infants will be found to have accessory adrenal tissue if closely studied. Because of the common ancestry of the adrenal gland, testis and ovary, disturbances of these glands are prone to produce heterosexual changes. Removal of adenoma of these glands causes a reversion to normal status.[15]

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[12] Morris, H.: Human Anatomy, ed. 9, edited by C. M. Jackson, Philadelphia, P. Blakiston's Son & Co., 1933.

[13] Prentiss, C. W., and Arey, L. B.: A Laboratory Manual and Text-Book of Embryology, ed. 3, Philadelphia, W. B. Saunders Company, 1920.

[14] Piersol, G. A.: Human Anatomy, ed. 2, Philadelphia, J. B. Lippincott Company, 1923, p 1801.

Histologic Structure.—By the end of the third year the adrenal cortex has differentiated into three distinct zones, these being from the capsule inward: the zona glomerulosa, the zona fasciculata and the zona reticularis. The zona reticularis is adjacent to the medulla. The entire cortex varies in thickness from 0.25 to 1.25 mm. The capsule sends small connective tissue septums into the cortex, which serves as a framework.

The cells of the zona glomerulosa are described by Piersol as being polyhedral and arranged in rounded masses of tortuous groups of cells. Cells of the zona fasciculata are parallel—a radially arranged group of cells. The zona reticularis is narrower than the other zones, and it is formed by the union of the inner ends of the columns of the zona fasciculata. Cells of the zona reticularis have been described by Piersol[16] as being from 15 to 20 microns in diameter. The cytoplasm contains variable amounts of fat granules, which are especially abundant in the zona fasciculata, there being few or none in the zona reticularis. This is such a noticeable finding in the zona fasciculata that the term "spongiocytes" has been applied to cells of this zone.

The adrenal cortex has the richest blood supply of any organ of the body, from 6 to 7 cc. of blood per minute per gram of tissue passing through it.[17] The source of this blood is from the right and left adrenal arteries, which arise directly from the aorta and anastomose freely within the gland. The capillaries are large and sinusoidal and pass into veins which join into a central vein at the hilus. The venous walls of the cortex vary in thickness and in some places are but one or two cells thick. The adrenal gland is innervated chiefly by the splanchnic nerves, these fibers penetrating the capsule with the connective tissue fibers and infiltrating the cortex.

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[15] Walters, Waltman; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome with Presentation of Ten Cases, Ann. Surg. **100**:670-688 (Oct.) 1934.

[16] Piersol, G. A.: Normal Histology, ed. 12, Philadelphia, J. B. Lippincott Company, 1920.

[17] Maximow, A. A., and Bloom, William: A Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1930, p. 704.

PATHOLOGIC ADRENAL CORTEX

Ewing[18] has arbitrarily classified tumors of the adrenal cortex into: (1) hyperplasia, nodular or diffuse; (2) adenoma, and (3) carcinoma.

Various grades of hyperplasia can be observed. Virchow[19] called this condition "struma suprarenalis;" he made no attempt to differentiate the nodular and the diffuse type. The nodular type is usually well encapsulated, and frequently many areas of hyperplasia can be found in one gland. The diffuse type has recently been more commonly associated with the picture of hirsutism.[15] The cells in diffuse hyperplasia resemble those of the zona glomerulosa; rarely do they simulate those of the zona fasciculata, although the cells in any zone may in part be duplicated. Nodular hyperplasia may be associated with nodules in the liver, and sexual overdevelopment may be seen in this type of condition.

Ewing stated that true adenoma can be distinguished from hyperplasia by its atypical and neoplastic structure. According to him, this is borne out in the so-called adenoma malignum, which is a carcinoma in a previously benign adenoma, and is of rather frequent occurrence. I have studied one such case. Adenoma of the adrenal gland usually occurs singly, but there may be multiple and bilateral growths. The tumor frequently projects from the capsule as a reddish or yellow structure, which is well circumscribed. Hemorrhage and central softening may occur. Some adenomas weigh as much as 4 ounces (114 Gm.) and still retain the characteristics of a benign adenoma. On occasions the adenoma is invaded by fibrous tissue, to the extent that it becomes quite firm and, as a result, is called a "fibro-adenoma." There is a tendency toward hyperchromatism of the nuclei in the true adenoma.

The occurrence of carcinoma of the adrenal gland is not so surprising when one considers the mesothelial origin of the cortex. It is this type of tumor that frequently produces secondary sexual changes.[20] The cells of such a carcinoma may resemble those of any of the layers of the cortex, although most frequently the cells of the zona fasciculata

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18. Ewing, James: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 770.

19. Virchow, cited by Wolley, P. G., and Adami, J. G.: A Primary Carcinomatoid Tumor (Mesothelioma) of the Adrenals, with Sarcomatous Metastases, Tr. A. Am. Physicians **17**:627-643, 1902.

20. Keyser, L. D., and Walters, Waltman: Carcinoma of the Suprarenal Associated with Unusual Endocrine Manifestations, J. A. M. A. **82**:87-88 (Jan. 12) 1924.

are simulated. Metastasis is very common, the usual sites being the lungs, liver, adjacent peritoneal lymph nodes and more distant organs. The carcinoma has a tendency to grow rapidly because of its rich blood supply, and the degenerative changes within it are quite common, especially hemorrhage and necrosis.

The carcinoma may attain enormous proportions, Cabot[21] having reported a case wherein the tumor was found to weigh 6 pounds (2,722 Gm.). Hirsutism accompanied the symptoms at the onset.

Because of the large size and early incorporation into the adjacent kidney, much discussion has arisen as to the origin of such a tumor, whether renal or adrenal. Glynn,[22] in an exhaustive study of the adrenal cortex, tended to disagree with those who felt that the renal hypernephroma was primary in adrenal rests. He gave his reasons as being (1) that there was a dissimilarity in the microscopic structure of the two, (2) that the renal hypernephroma apparently never influences growth or sexual characteristics and (3) that it was difficult to explain why adrenal rests, although rather rare in the kidney, should produce such a common tumor as the hypernephroma, which is by far the most common renal tumor, whereas adrenal rests in other organs, which are common, especially in early life, should produce a tumor so infrequently.

The metastatic involvement produced by carcinoma of the adrenal cortex differs from that produced by the so-called renal hypernephroma in that in the case of the former bone is rarely involved, whereas in the case of the latter such involvement is frequent. Lescher and Robb-Smith[23] reported a case of tumor of the adrenal cortex associated with hirsutism in which the entire gland was destroyed. The tumor weighed 593 Gm. and was covered with a thin, yellowish capsule. Holmes[24] described a tumor weighing 1,025 Gm.; subsequent cure of the preexisting hirsutism followed its removal. Glynn examined the specimen and reported a similarity between its cells and those of the zona reticularis. He stated that the cells measured from 20 to 25 microns in diameter and their nuclei from 8 to 9 microns in diameter as compared to 15 microns for the entire cell and 7 microns for the nuclei of normal adult cells fixed in a solution of formaldehyde.

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[21] Cabot Case Records of the Massachusetts General Hospital, New England J. Med. **208**:546-552 (March 9) 1933.

[22] Glynn, E. E.: The Adrenal Cortex, Its Rests and Tumours: Its Relation to Other Ductless Glands, and Especially to Sex, Quart. J. Med. **5**:157-192 (Jan.) 1912.

[23] Lescher, F. G., and Robb-Smith, A. H. T.: History of a Case of Carcinoma of the Cortex with Cushing's Syndrome, Proc. Roy. Soc. Med. **27**:404-408 (Feb.) 1934.

[24] Holmes, Gordon: A Case of Virilism Associated with Suprarenal Tumour: Recovery After Its Removal, Quart. J. Med. **18**:143-152 (Jan.) 1925.

RESULTS OF STUDY

The average areas of the nuclei and nucleoli were calculated from actual measurements of the nuclei and nucleoli of 20 individual cells in each specimen.

In normal adrenal tissue the areas of the nuclei of cells in the zona glomerulosa varied from 10.09 to 54.51 square microns, whereas the areas of the nucleoli varied from 0.545 to 2.417 square microns. The average area of the former was 30.79 square microns, and that of the latter was 1.297 square microns.

As a result of a study of the zona fasciculata of ten histologically normal adrenal cortices, the nuclei were found to vary in size from 18.17 to 34.32 square microns, and the nucleoli, from 0.545 to 1.27 square microns. The average area of the former was 25.17 square microns, and that of the latter was 0.871 square micron.

As a result of a study of the zona reticularis of ten histologically normal cortices, the nuclei were found to vary in size from 36.35 to 56.54 square microns, and the nucleoli, from 1.26 to 2.52 square microns. The average area of the former was 43.57 square microns, and that of the latter was 1.78 square microns.

In specimens of tissue from a series of growths diagnosed as adenoma of the adrenal cortex and from an adrenal cortex with hemorrhagic inflammation, the smallest average area of the nuclei was 29.61 square microns, and the largest average area of the nuclei was 50.97 square microns. The smallest average area of the nucleoli was 1.17 square microns, and the largest average area of the nucleoli was 3.22 square microns. The actual areas of the nuclei varied from 20.15 to 90.67 square microns, whereas the actual areas of the nucleoli varied from 0.755 to 6.09 square microns. It will be seen that the average area of the nuclei is 37.87 square microns, and that of the nucleoli is 1.95 square microns.

In tissue from growths diagnosed as carcinoma the nuclei ranged in area from 34.21 to 218.10 square microns. The nucleoli varied in area from 1.46 to 65.43 square microns. The average area of the nuclei was found to be 82.18 square microns, and that of the nucleoli was 8.50 square microns.

Considering the group of normal or benign cells in contrast to the group of carcinoma or malignant cells, it is evident that both the nuclei and the nucleoli of malignant cells are larger than those of benign cells. Examination of the results obtained by measuring the size of the nuclei and nucleoli of benign and of malignant cells of the adrenal cortex shows that although both the nuclei and the nucleoli of malignant cells are larger than those of benign cells, the nucleolus of the malignant cell is relatively much enlarged.

With the average measurements of the nuclei and nucleoli of cells of the normal adrenal cortex as 49.76 and 1.97 square microns, respectively, the ratio of the size of the nuclei to that of the nucleoli is found to be 25.2: 1; with the average measurements of the nuclei and nucleoli of adrenal adenoma cells as 37.87 and 1.58 square microns, respectively, the ratio is found to be 23.9: 1; with the average measurements of the nuclei and nucleoli of cells of the adrenal cortex with hemorrhagic inflammation as 32.04 and 1.51 square microns, respectively, the ratio is found to be 21.2: 1, and with the average measurements of the nuclei and nucleoli of adrenal carcinoma cells as 82.14 and 8.50 square microns, respectively, the ratio is found to be 9.67: 1. Thus, there is seen to be a characteristic relationship between the size of the nuclei and the nucleoli of benign and malignant cells.

In the histogram showing the sizes of the nuclei (fig. 1) it will be seen that approximately 85 per cent of the nuclei of benign cells fall within the areas of from 30 to 60 square microns; all measure greater than 10 square microns, and the average area is 49.76 square microns. Approximately 85 per cent of the nuclei of malignant cells fall within the measurements of from 40 to 140 square microns, the average area being 82.14 square microns. All measure greater than 30 square microns. Furthermore, 90 per cent of the nuclei of adenoma cells fall within the measurements of from 20 to 50 square microns, the average area being 37.87 square microns. All measure more than 20 square microns. Thus, it is seen that the average size of the nuclei of benign and of malignant cells differ, although there is some overlapping in size when the nuclei of malignant and of benign cells are not differentiated.

Average Measurements of Nuclei and Nucleoli in Various Types of Adrenal Tissue

Adrenal Tissue	Average, Area, Square Microns		Ratio of Nuclei to Nucleoli
	Nuclei	Nucleoli	
Normal adrenal tissue (cortex)	49.76	1.97	25.2:1
Adenomatous tissue	37.87	1.58	23.9:1
Tissue with hemorrhagic inflammation	32.04	1.51	21.2:1
Carcinomatous tissue	82.14	8.50	9.67:1

In the histogram presenting the sizes of the nucleoli (fig. 2) it will be seen that 100 per cent fall within the areas of from 0.5 to 2.5 square microns, the average size being 1.97 square microns. The nucleoli of adenoma cells vary from 0.5 to 6 square microns, and approximately 85 per cent fall between 1 and 2.5 square microns. Of the nucleoli of carcinoma cells, 68 per cent fall within the range of 2 and 15 square microns, 45 per cent being between 5 and 15 square microns. The average size of these nucleoli is 8.5 square microns. Thus it is seen that when one

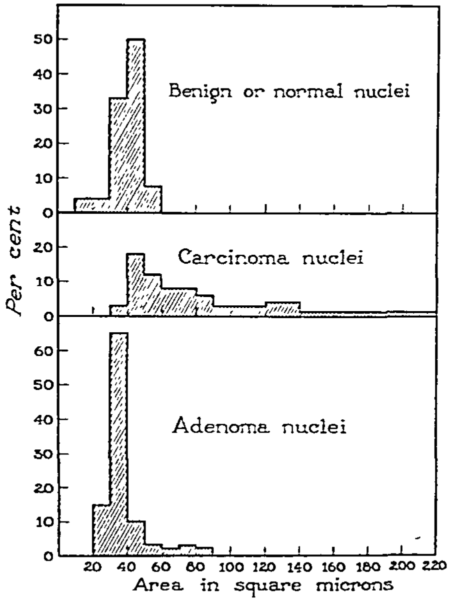

Fig. 1.—Chart showing the percentage distribution and area of nuclei.

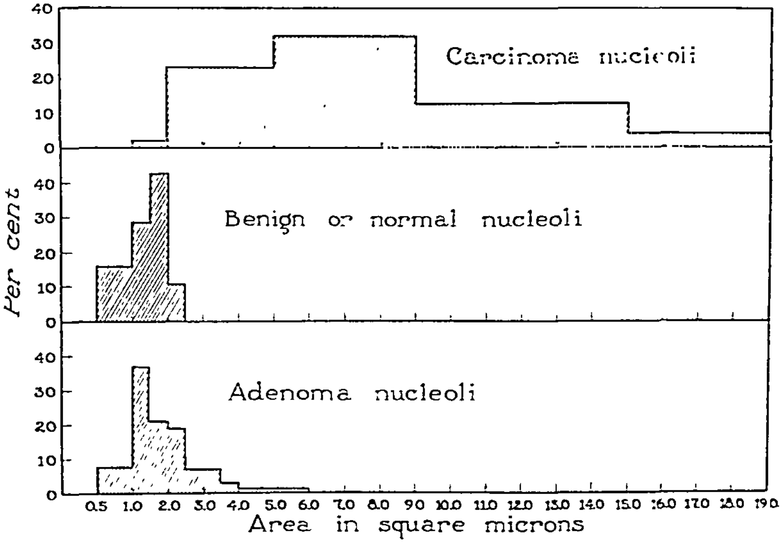

Fig. 2.—Chart showing the percentage distribution and area of nucleoli.

compares the size of the nucleoli of benign cells with that of the nucleoli of malignant cells, there is much less overlapping than when one compares the size of the nuclei of benign cells with that of the nuclei of malignant cells.

It appears, therefore, that the size of the nucleoli is a far better criterion of malignancy than the size of the nuclei and whereas the nuclei of malignant cells are larger than those of benign cells, the nucleoli of malignant cells are relatively enlarged much more than those of benign cells (figs. 3 and 4). With the average measurements of the nuclei and nucleoli of malignant cells as 82.14 and 8.05 square microns, respectively, the ratio of the size of the nuclei to that of the nucleoli is found to be 9.67:1; with the average measurements of the nuclei and nucleoli of benign cells as 49.76 and 1.97 square microns, respectively, the ratio is found to be 25.2:1, and with the average measurements of the nuclei and nucleoli of adenoma cells as 37.87 and 1.58 square microns, respectively, the ratio is found to be 23.9:1. On examining these data it can be seen, therefore, that there is a characteristic relationship between the size of the nuclei and nucleoli of benign and malignant cells of the adrenal cortex.

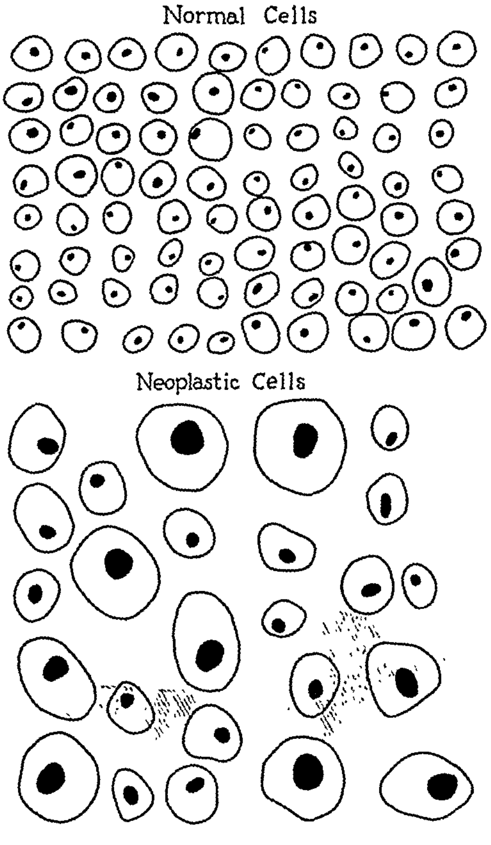

Fig. 3.—Normal and neoplastic cells.

SUMMARY

Twenty cells in each specimen of tissue from four adrenal carcinomas, four adenomas and one adrenal gland with hemorrhagic inflammation and from ten specimens of normal adrenal tissue were studied with particular reference to the size of the nucleus and nucleolus of each cell.

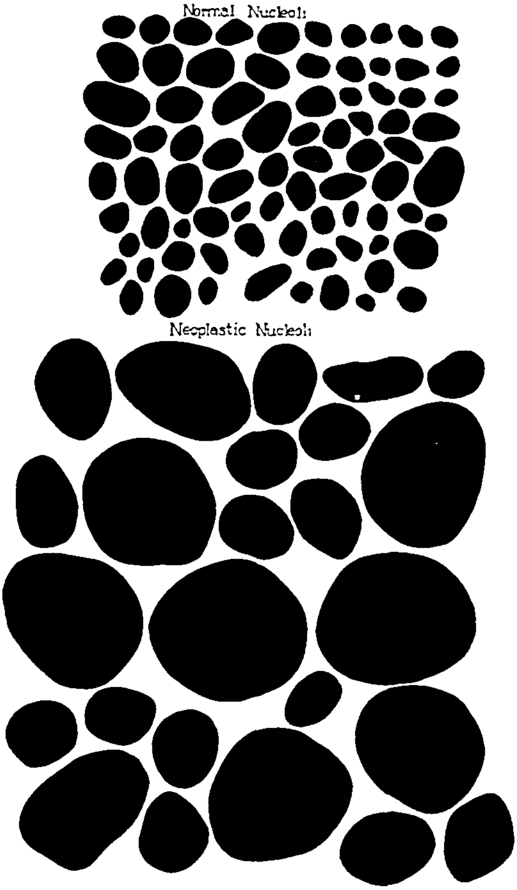

Fig. 4.—Normal and neoplastic nucleoli.

In malignant tissue the average area of the nuclei was 82.14 square microns; in adenomatous tissue it was 37.87 square microns, and in normal adrenal tissue it was 49.76 square microns.

In malignant tissue the average area of the nucleoli was 8.50 square microns; in adenomatous tissue it was 1.58 square microns, and in normal adrenal tissue it was 1.97 square microns.

The ratio of the size of the nuclei to that of the nucleoli in malignant cells was 9.67 : 1 ; in adenoma cells, 23.9 : 1, and in normal adrenal cells, 25.2 : 1.

CONCLUSIONS

The nuclei and nucleoli of malignant cells are larger than those of benign cells. The ratio between the size of the nuclei and the size of the nucleoli in malignant cells is much smaller than that which exists between the size of the nuclei and the size of the nucleoli of benign cells.

MYELOMA AND ITS NEURAL COMPLICATIONS

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AND
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The most frequent neural complications of the myeloma are those referable to the spinal cord and roots. The almost constant involvement of the spinal vertebrae in this disorder readily explains the neural manifestations. The pressure exerted by the invading neoplasm on the spinal cord or by the diseased vertebrae on the vessels of the spinal cord leads to a myelopathic process, thus interfering with the normal conduction of neural impulses of the various fiber tracts. The occurrence of root pains, herpes zoster or peripheral neuritis is the end-result of direct pressure on the roots of the spinal cord, the spinal ganglions and the peripheral nerves. Although metastases to the bones of the skull are frequent, mental symptoms and other signs of cerebral involvement are rarely observed. Compression of the cerebral structures by the metastases to the skull, apparently, is not sufficient to elicit neurologic symptoms.

The rarity of the disease is evidenced by its presence only 3 times in 4,000 autopsies at the Bellevue Hospital (Symmers and Vance[1]) and in 4 instances in 9,000 autopsies at the Johns Hopkins Hospital. In a series of 20,000 patients admitted to the Montefiore Hospital, 12 had myeloma. Of this group, 6,500 came to autopsy, and myeloma was found in 9 instances. The brain and spinal cord were examined in 6 of these cases. Neurologic signs and symptoms secondary to cranial or vertebral involvement were noted in all 12 cases.

This presentation is of interest because of the large number of cases, the direct metastasis to the spinal dura in 1, the involvement of the peripheral nerves in another and the presence of a psychosis in a third instance. Metastasis to the spinal dura and involvement of the peripheral nerves, as far as we know, have not been described in the literature.

REPORT OF CASES

Neural Complications with Cranial or Vertebral Involvement and Removal of the Brain and Spinal Cord.—CASE 1.—D. B., a man aged 52, was admitted to the

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From the Neuropathological Laboratory and the Neurological Division, the Montefiore Hospital.

[1] Symmers, D., and Vance, D.: The Multiple Myelomata and Their Ability to Metastasize, Ann. Surg. **67**:687, 1918.

Montefiore Hospital on Aug. 20, 1931, with a history of constant pain in the midthoracic region for several months, followed by girdle pains and transitory sharp, shooting pains in the lower extremities. In August 1931 there appeared numbness and weakness of both lower extremities followed by complete paraplegia. At about the same time he suffered from constipation, difficulty in starting the urinary stream and reduction in libido. The past history was unimportant, except for the contraction of a chancre in 1900, for which he received antisyphilitic treatment.

Examination.—The blood pressure was 145 systolic and 105 diastolic. A small kyphus was noted at the fourth dorsal vertebra. There was paraplegia with total loss of power in the lower extremities. The deep reflexes of the lower extremities were exaggerated, and there was a Babinski toe sign bilaterally. All forms of sensation were diminished below the fifth dorsal segment.

Laboratory Data.—The urine contained a slight trace of albumin with occasional granular casts. The Bence-Jones protein was not determined. The spinal fluid contained 30 polymorphonuclear leukocytes and 10 lymphocytes and gave a positive reaction to the Pandy test. Manometric studies revealed no evidence of block. Roentgen examination of the spine showed collapse of the ninth dorsal vertebra (fig. 1). The examination of the blood, including chemical studies, gave negative results.

Course.—During the patient's entire stay in the hospital he received large doses of morphine for relief from the intractable pain. On August 25 he became comatose, the blood pressure dropped to 110 systolic and 70 diastolic, a paralytic ileus developed and he died on August 26.

Clinical Diagnosis.—The diagnosis was myeloma of the dorsal vertebrae with compression of the cord.

Autopsy.—Gross Examination: The bodies of the seventh to the ninth dorsal vertebrae were infiltrated by tumor tissue; the ninth dorsal vertebra was fractured (fig. 1). The spinal cord at this level was adherent to the posterior part of the fractured vertebra. The anterolateral surface of the spinal dura was markedly thickened between the sixth and the ninth dorsal segment, and the posterolateral surface was slightly thickened.

Microscopic Examination: Sections of the cord at various levels were embedded in pyroxylin, cut and stained by the myelin sheath, cresyl violet and hematoxylin and eosin methods. In the sections stained by the myelin sheath method, the anterior surface of the spinal dura at the sixth dorsal segment was extensively thickened and was invaded by neoplastic tissue (fig. 2). The fiber tracks appeared to be intact. Under higher power magnification, however, demyelinization of several areas in the anterior columns of the cord was observed. The ventral and dorsal spinocerebellar pathways had a slight honey-combed appearance. There was also demyelinization of the ventral surface of the posterior column of the eighth dorsal segment. The axis cylinders at this level, except for those of the lateral corticospinal tract which were swollen, showed no changes. The anterior and posterior spinal vessels were slightly compressed. The right lateral spinal artery was slightly thickened, and its lumen was constricted. The anterior horn cells disclosed slight retrograde changes, and their Nissl substance stained poorly. Sections above and below the compression did not show any evidence of ascending or descending degeneration.

The tumor consisted of numerous plasma cells and a few giant cells with little stroma (fig. 3). In some areas inflammatory cells, essentially polymorphonuclear leukocytes, were scattered between the plasma cells. The loosely packed plasma cells were round, oval and polygonal, with homogeneous, pale neutrophilic cytoplasm. Some had a single nucleus, while others were multinucleated. Zones of necrosis were observed, and a few small spicules of bone were found.

Comment.—The patient had root pains for months prior to admission to the hospital. Later there suddenly developed symptoms and signs of a lesion at the level of the fifth and sixth dorsal segments. The neurologic symptoms were the result of compression of the cord by the metastatic myeloma to the spinal dura at that level and not by the fractured dorsal vertebra. It is somewhat difficult to explain the slight impairment of the circulation of the vessels of the spinal cord with such marked invasion of the dura. The early death of the patient after the sudden paraplegia most likely prevented severe impairment of the circulation of the spinal cord and the production of a marked myelopathic process.

Fig. 1 (case 1).—Roentgenogram showing collapse of the eighth and ninth dorsal vertebrae.

Case 2.—M. S., a married man aged 43, was admitted to the Montefiore Hospital on Jan. 24, 1931, with a history of shooting pains in the right thoracic region radiating down the right lower extremity since June 1929. The pain became progressively worse, and the patient was subjected to laminectomy in October 1930. After this there gradually developed weakness in both lower extremities and inability to walk.

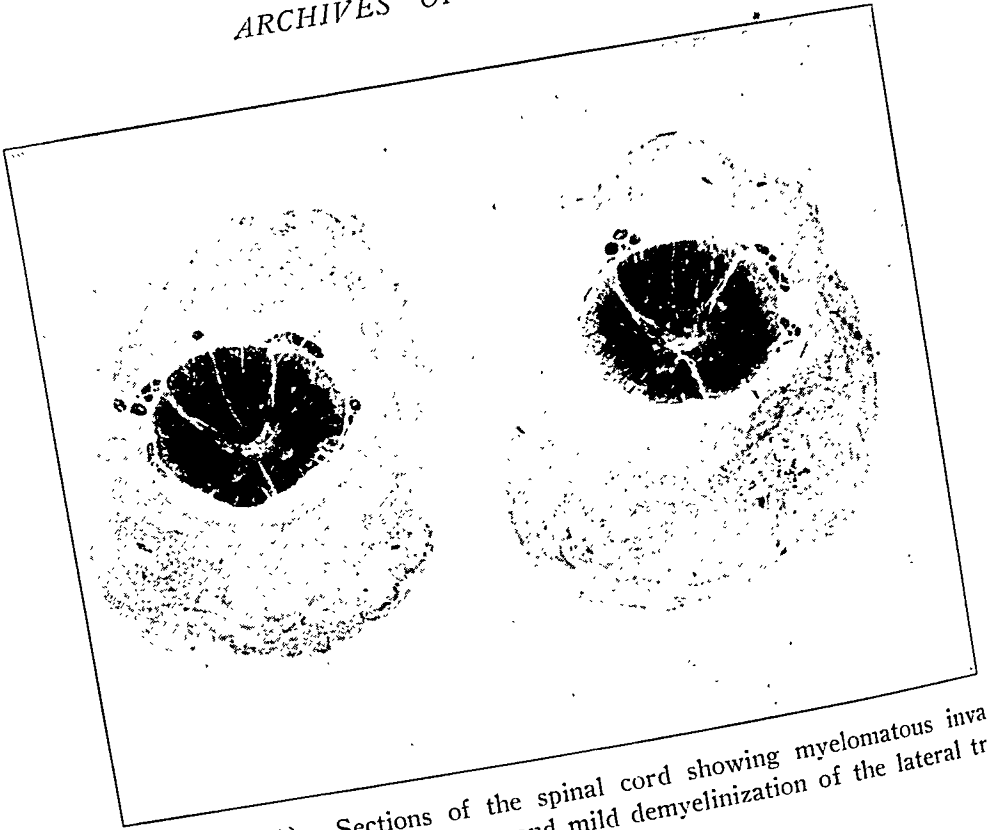

Fig. 2 (case 1).—Sections of the spinal cord showing myelomatous invasion of the thickened ventral spinal dura and mild demyelinization of the lateral tracts. Myelin sheath stain.

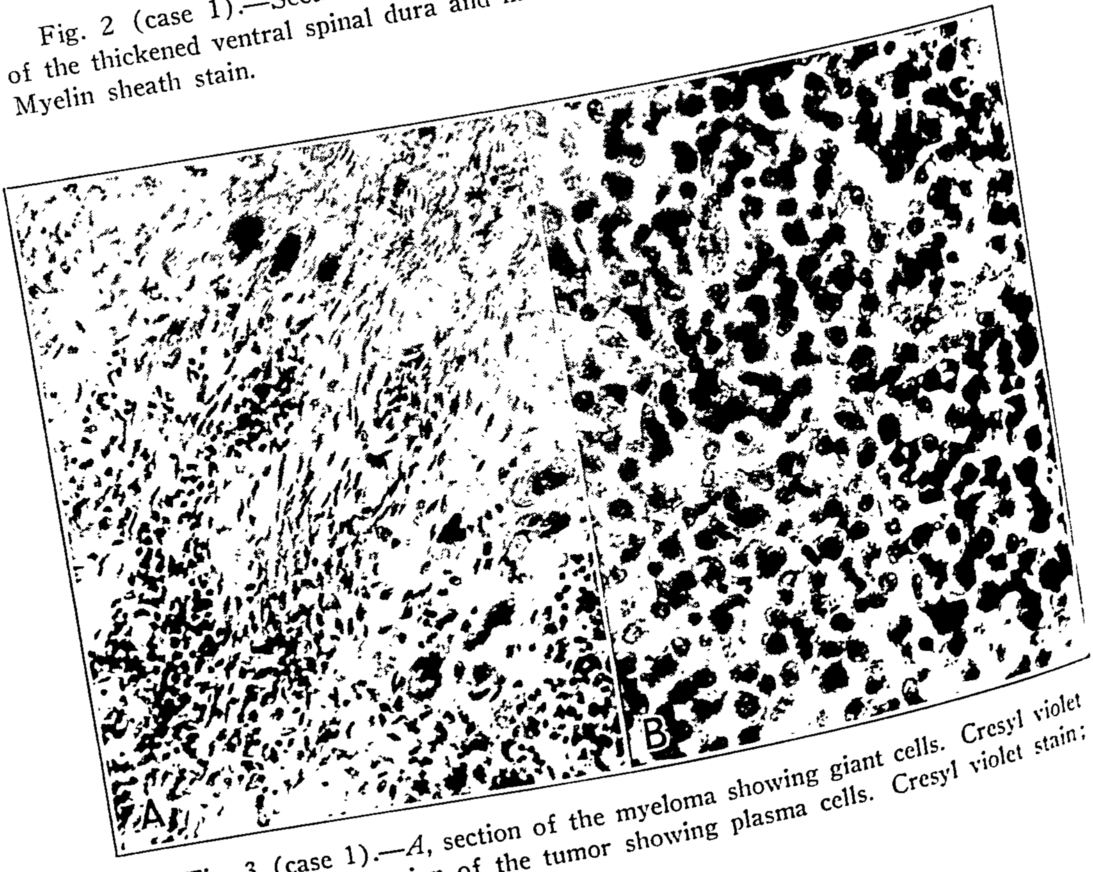

Fig. 3 (case 1).—*A*, section of the myeloma showing giant cells. Cresyl violet stain; × 150. *B*, section of the tumor showing plasma cells. Cresyl violet stain; × 300.

Examination—The results of the general physical examination were negative. Neurologic examination revealed a flaccid paraplegia, loss of power in the lower extremities, generalized hyperreflexia, a Babinski toe sign bilaterally and allied responses. Percussion and pressure on the dorsal and lumbar vertebrae produced severe pain. There was a belt of hyperalgesia and hyperthermesthesia at the eleventh and twelfth dorsal dermatomes, with diminution of all forms of sensation below that level. The patient had slight difficulty in starting the urinary stream.

Laboratory Data.—Examination of the blood revealed a moderate secondary anemia. On repeated examinations the urine showed heavy traces of albumin. The presence of Bence-Jones bodies was not determined. The Wassermann reaction of the blood and spinal fluid was negative. The response to the gum mastic test was 0244443200. Manometric studies revealed no evidence of block. Roentgen examination of the vertebral column disclosed collapse of the twelfth dorsal vertebra (fig. 4).

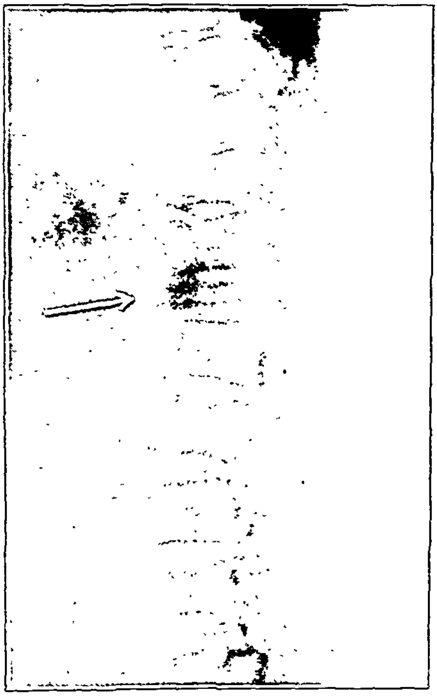

Fig. 4 (case 2).—Roentgenogram showing collapse and destruction of the twelfth dorsal vertebra.

Course.—Shortly after the patient's admission lobar pneumonia developed, from which he recovered. Roentgen examination on May 20 disclosed destruction of several of the thoracic vertebrae with partial collapse of the bodies of the third, fourth and fifth thoracic vertebrae. He received high voltage roentgen therapy to the vertebrae, with some relief from pain. Bronchopneumonia developed, and the patient died on August 28.

Clinical Diagnosis.—The diagnosis was myeloma of the dorsal vertebrae with compression of the cord.

Autopsy.—Gross Examination: The posterior part of the body of the twelfth dorsal vertebra was carious and spongy and replaced by islands of necrotic tissue. The spinal dura at this level was slightly thickened and compressed by the vertebra. The cord was cut transversely, and no abnormalities were encountered. There were no metastases to the other organs.

Microscopic Examination: Sections from various regions of the cord were embedded, cut and stained by the myelin sheath and cresyl violet methods. There was demyelinization of the posterior columns of the third lumbar segment and less demyelinization of the lateral columns and posterior roots (fig. 5). This demyelinization was also present to a slight degree in the lower thoracic and upper lumbar regions. The lateral surface of the dura of the third lumbar segment was thickened (fig. 5) and invaded by bony tissue. The lateral spinal arteries were slightly thickened, had narrow lumens and were compressed by the thickened dura.

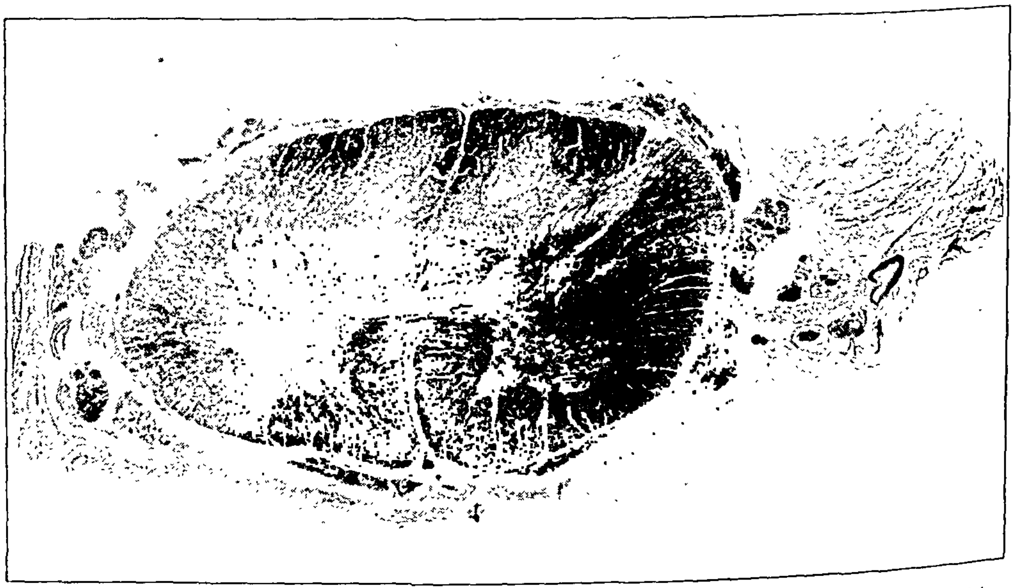

Fig. 5 (case 2).—Section of the spinal cord showing the thickened dura with bony invasion on its lateral aspect and degeneration of the spinal tracts, most marked in the posterior columns. Myelin sheath stain.

Under higher power magnification the posterior columns showed varying degrees of destruction of the myelin sheaths. The anterior horn cells were well preserved except for an occasional ganglion cell in the lower dorsal and upper lumbar regions, which was poorly stained. Segments above this level showed an ascending degeneration of the posterior columns.

The vertebral tumor consisted of loosely and closely packed round, polygonal and oval cells with a homogeneous bluish cytoplasm. The nuclei were large, round and very dark. Most of them were eccentrically placed. Some of the cells were slightly compressed and spindle shaped. Many multinucleated giant cells were seen. The cells were embedded in a hyaline matrix, in which there was also an occasional fat globule.

Comment.—The myeloma found at the twelfth dorsal vertebra and the thickened dura compressed the vessels of the spinal cord at that level. The neurologic picture was that of a level lesion with motor and sensory disturbances due to vascular obstruction. The excruciating pains produced by pressure on the posterior roots were relieved by high voltage roentgen therapy. Of interest was the lack of improvement in the symptoms after the laminectomy.

Case 3.—O. B., a married man aged 68, was admitted to the Montefiore Hospital on Oct. 30, 1926. In 1922 he had an attack of lumbago. One year later he experienced severe pain in the lumbar region and pain and a sensation of coldness in the lower extremities. In February 1926 he had urinary retention necessitating catheterization. On admission he was unable to sit or walk because of intense pain across the back and in the lower extremities.

Examination.—There was cardiac enlargement to the left with a mitral systolic murmur. The blood pressure was 130 systolic and 65 diastolic. There was a palpable tender pulsating mass in the middle of the left lumbar region. Neurologic examination disclosed weakness of the left lower extremity, diminished knee and ankle jerks, absence of the right lower abdominal reflex and loss of all forms of sensation below the twelfth dorsal dermatome.

Laboratory Data.—Roentgen examination of the dorsal region of the spine disclosed atrophy of the bone. There were partial destruction and forward dislocation of the second and fourth lumbar vertebrae and complete destruction of the third lumbar vertebra; these vertebrae were surrounded by a mass. There was also a pathologic fracture of the right clavicle. The urine contained heavy traces of albumin, occasional white and red blood cells and hyaline and granular casts. Tests for Bence-Jones protein were negative on several occasions. The blood and spinal fluid were normal.

Course.—Hypostatic bronchopneumonia developed, and the patient died on Jan. 14, 1927.

Clinical Diagnosis.—The diagnosis was vertebral myeloma compressing the spinal cord and cauda equina and metastases to the clavicle and ribs.

Autopsy.—Gross Examination: There was a large encapsulated soft fluctuating vascular mass in the region of the left second to the fifth lumbar vertebrae, which extended 4 cm. to the left of the spinal column posteriorly and from 1 to 2 cm. to the right. The tumor did not extend anteriorly beyond the ligaments of the surfaces of the vertebrae; posteriorly it reached to the spinous processes on both sides. Longitudinal sections through the third and fourth lumbar vertebrae revealed a large vascular and necrotic tumor and small scattered tumor nodules almost entirely replacing the vertebral bodies and spinous processes. The spinal canal was narrowed by the tumor, and the cord and cauda equina at this level were compressed. The dura and cord were not invaded by the neoplasm. The right clavicle and the sixth left rib were invaded by tumor nodules.

Microscopic Examination: Except for a narrowing of the lumens of the spinal vessels and destruction of occasional myelin fibers of various tracts, the spinal cord appeared to be normal.

The tumor was highly vascular and consisted of compact polygonal cells with small round nuclei and uniformly relatively pale staining cytoplasm; the stroma was scanty. There were innumerable cells which closely resembled the plasma cell type of myelocyte.

Comment.—The neurologic signs and symptoms in this case were essentially due to the compression of the lumbar region of the spinal cord and its vessels and the cauda equina. The radicular pains were the most outstanding feature. The spinal dura and cord, in contrast to those in cases 1 and 2, were not invaded by the tumor.

CASE 4.—H. S., a man aged 46, entered the Montefiore Hospital on Nov. 26, 1930, with a history of slight pain in the right ribs for fourteen years. Seven years later removal of part of the fourth right rib led to a diagnosis of myeloma. In November 1929 the patient experienced severe pain in the left ribs, back, thighs and legs. There was slight improvement in the symptoms after high voltage roentgen therapy. In June 1930 he complained of headaches.

Examination.—On the patient's admission to the hospital there were observed a slight limitation of the motion of the head and neck and tenderness on percussion over the cervical and lumbar regions of the spine. There was a slight secondary anemia. The roentgenograms showed scattered areas of osseous destruction in the skull and in both scapulas and both femurs. The patient received high voltage roentgen therapy and was discharged in March 1931 as slightly improved.

On readmission to the hospital on April 25, 1931, he complained of headache, pain in the neck and chest and inability to straighten out his back.

Laboratory Data.—Roentgen examination revealed almost complete destruction of the body of the first lumbar vertebra. There was severe anemia, as indicated by 1,900,000 red cells, 5,200 white cells and a hemoglobin content of 30 per cent. The total serum protein, which was 7.65 Gm. per hundred cubic centimeters (albumin, 4.04 Gm.; globulin, 3.61 Gm.), decreased to 3.61 Gm. (albumin, 2.53 Gm.; globulin, 1.08 Gm.). The urine showed albumin, Bence-Jones protein and many granular casts. The Congo red test was positive for amyloidosis on Feb. 4, 1932.

Course.—The patient was put on a high caloric, high protein, high salt diet with unlimited fluids, and within two weeks the serum protein content rose to 4.73 Gm. (albumin, 3.22 Gm.; globulin, 1.51 Gm.). At no time was the patient edematous. Dorsal and sacral decubitus ulceration developed, followed by a rise in temperature to 102.4 F. On February 22 the patient became very weak and was unable to stand, sit or turn from side to side, with complete loss of power in all extremities. Neurologic examination at this time disclosed diminished reflexes of the upper extremities, hyperactive knee jerks and absence of the left ankle jerk and of the abdominal and cremasteric reflexes. Bronchopneumonia developed, and death occurred on February 24.

Clinical Diagnosis.—The diagnosis was vertebral myeloma, with compression of the cord, and myelomas of the skull, clavicle and ribs.

Autopsy.—Gross Examination: The essential lesions were found in the skeletal system. The calvarium was thin and transparent. Its inner table and, in places, its outer table were studded with circumscribed peculiar grayish red to grayish brown areas. The base of the skull was similarly involved. Several ribs were fractured, and on sectioning the cut surface showed either pale fat marrow or a few localized glistening grayish yellow gelatinous areas. The bodies of the eighth and ninth dorsal, sacral and some of the coccygeal vertebrae were fractured, and the fragments were dislocated. These vertebrae were destroyed, and were replaced by hemorrhagic and peculiar grayish red gelatinous masses. The spinal cord was not removed.

in the arms since January 1933. This was soon followed by a tingling sensation in the finger-tips and excruciating pains in the arms, fingers and hands. In June 1934 she experienced numbness and weakness of both hands. Prior to admission to this hospital, examination at the Mount Sinai Hospital revealed secondary anemia, mild peripheral neuritis of the upper extremities and a low grade fever, the temperature ranging from 100 to 102 F. The blood count disclosed a hemoglobin content of from 48 to 62 per cent, without any leukocytosis but some increase in monocytes.

Examination.—Physical examination disclosed pallor, a systolic murmur over the precordium, with its greatest intensity over the aortic area, and palpable lymph nodes in both axillae. Neurologic examination revealed bilateral atrophy of the thenar and hypothenar eminences and interossei muscles without fibrillations. There were diminished vibratory sensation in the toes and a smooth and atrophic tongue with marked tremor. The knee jerks were diminished but present. Position sense was retained.

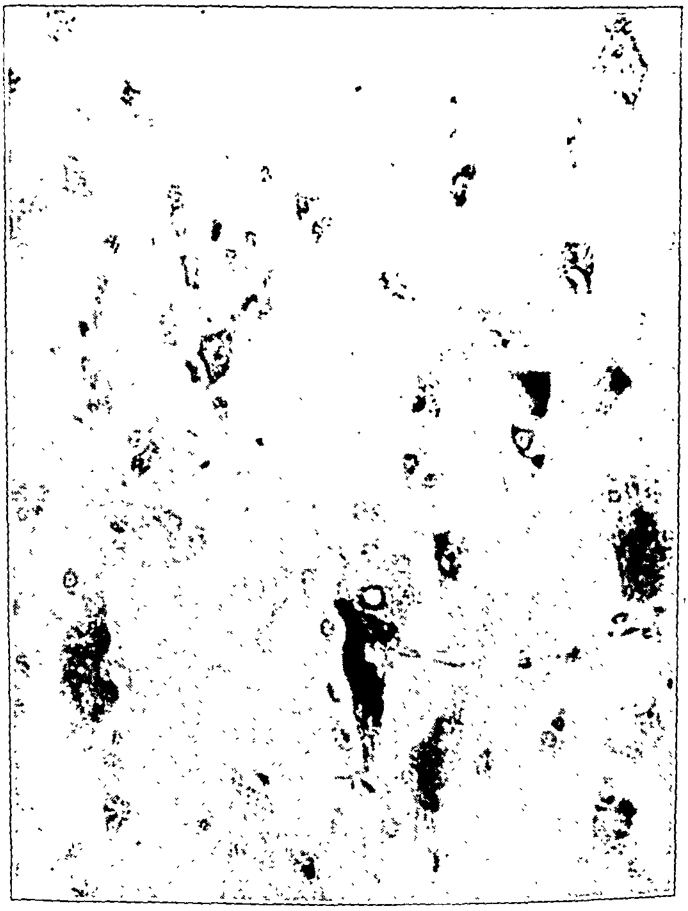

Fig. 8 (case 5).—Section of the cortex showing chromatolysis, vacuolation and degeneration of the giant pyramidal cells of Betz. Cresyl violet stain; × 200.

Laboratory Data.—The urine was positive for albumin but negative for Bence-Jones protein. Examination of the blood disclosed 2,800,000 red cells, 50 per cent hemoglobin and 9,800 white cells, with microcytosis, poikilocytosis and central pallor. The Wassermann reaction of the spinal fluid was negative. The reaction to the gum mastic test was 0000000000; the total protein content was 31.3 mg. per hundred cubic centimeters. Analysis of the gastric contents showed the presence of free hydrochloric acid. Roentgen examination disclosed absorption of bone in the outer third of the right clavicle, cloudiness of both antrums and a small circumscribed nodule in the lower lobe of the right lung.

Course.—The general weakness became progressively worse, and roentgen examination of the right elbow showed a destructive lesion of the lower end of the humerus. On August 2 the patient sustained a right supracondylar pathologic fracture. Soon after she became delirious, dyspneic and cyanotic and died on the same day.

Clinical Diagnosis.—The diagnosis was multiple myeloma and compression of the brachial plexus.

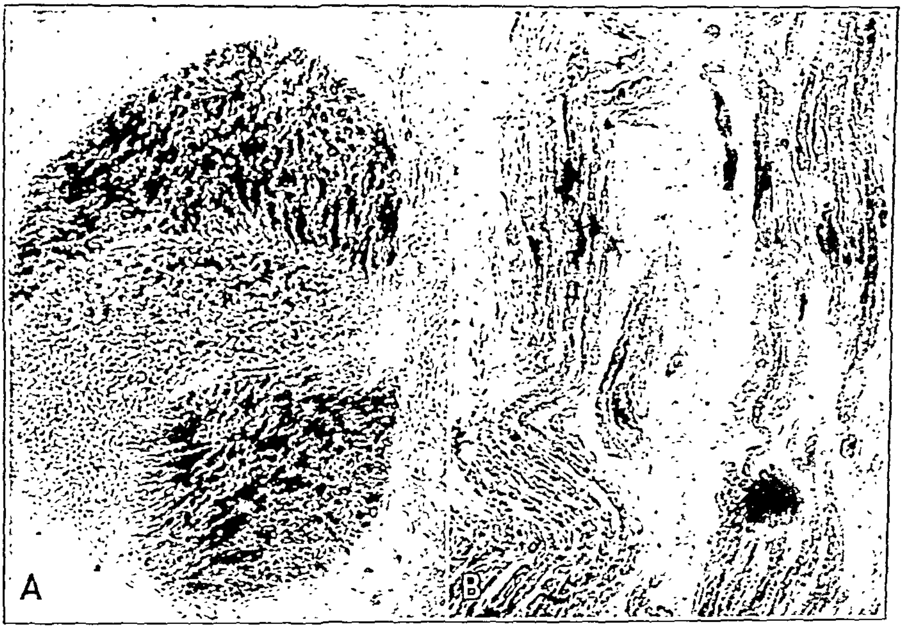

Fig. 9 (case 6).—*A*, section of the spinal cord showing partial destruction of the posterior root. Myelin sheath stain; × 128. *B*, section of the spinal cord showing disintegration of myelin in the nerve fibers of the brachial plexus. Sudan III stain; × 116.

Autopsy.—Gross Examination: The brain and spinal cord showed no gross abnormalities. The brachial plexus was removed, and sections were embedded.

Microscopic Examination: In sections through the medulla oblongata in the region of the twelfth nerve nucleus, a few of the nerve cells of the left hypoglossal nucleus were diminished in number and size and showed slight chromatolysis.

A section of the spinal cord, the eleventh dorsal segment, showed partial demyelinization of one of the posterior roots (fig. 9 *A*). In the preparation stained with cresyl violet the anterior horn cells in the cervical region of the spinal cord stained poorly. In the lower cervical region an occasional pyknotic anterior horn cell was noted.

There were occasional demyelinization of single fibers and breaking-down and disintegration of myelin within the nerves of both brachial plexuses (fig. 9 *B*). In the preparation stained with sudan III there were slight deposits of fat (fig. 9 *B*), while in the preparation stained by the Bielschowsky method the axis cylinders were slightly swollen and disintegrated.

Comment.—The diminution and slight pathologic changes within the nerve cells of the left hypoglossal nucleus were most likely due to the compression of the hypoglossal nerves with retrograde degeneration within its respective nerve cells. The other changes, such as bilateral atrophy of the thenar and hypothenar eminences and the diminished vibratory sense in the toes, were possibly caused by compression of the peripheral nerves and the roots. In the absence of myelomatous invasion of the peripheral nerves, the peripheral neuritis might have been secondary to the severe anemia or to some unknown toxic factors.

Neural Complications with Vertebral and Cranial Involvement.[2]—CASE 7.—H. S., a man aged 71, was admitted to the Montefiore Hospital on Aug. 11, 1929, with a history of having received a blow over the chest six months before. The next day he experienced excruciating pain in the lower part of the spine and the lower extremities and was confined to bed for several weeks. Later he also complained of pain in the right shoulder and the left side of the chest. The pains were somewhat relieved when he was lying down.

Examination.—There was a soft mass over the right clavicle near the sternal border. The expansion of the chest was poor. There was an area of bronchial breathing over the base of the right lung posteriorly and an area of diminished breathing with a few râles over the lower left side of the chest anteriorly. A systolic murmur was heard over the apex. The liver was about two fingerbreadths below the costal margin. There were tenderness over the lower vertebrae and kyphosis of the dorsal portion and part of the lumbar portion of the spine. The knee jerks were present and equal, but there was ankle clonus bilaterally without any pathologic reflexes. On August 17 the patient became markedly dyspneic and died on the same day.

Laboratory Data.—Roentgen examination showed numerous areas of destruction of the cranial bones. Areas of rarefaction were also seen in the ribs, lumbar vertebrae and pelvis. There were pathologic fractures of the ribs. Examination of the blood revealed 1,720,000 red cells, 7,800 white cells and 30 per cent hemoglobin. The urine was positive for albumin but negative for Bence-Jones protein.

Clinical Diagnosis.—The diagnosis was multiple myeloma.

Autopsy.—Gross Examination: Numerous myelomatous masses were found in the bony structures, as revealed at the roentgen examination. The portions of the body of the lower lumbar vertebrae and of the left innominate bone showed an extensive replacement of marrow by tumor tissue. The brain and spinal cord were not removed.

Microscopic Examination: The diagnosis on the basis of the microscopic picture was myeloma.

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[2] Autopsy was performed in some of these cases, but the brains and cords were not removed.

Comment.—Although the lumbar vertebrae and the skull were riddled with myelomatous masses, the neurologic signs, except for ankle clonus bilaterally, were negative. Apparently, the compression of the vessels of the spinal cord by the tumor was insufficient to have caused a myelopathic process. The excruciating pains in the lower extremities were undoubtedly due to compression of the roots by the vertebral metastases. High voltage roentgen therapy was not administered, as the patient died shortly after his admission to the hospital.

CASE 8.—L. S., a woman aged 58, was admitted to the Montefiore Hospital on Oct. 6, 1931, with a history of pain in the left shoulder since 1924. Six years later there appeared a lump in the upper left side of the chest. The patient experienced pains in the upper and lower extremities, which were aggravated by any motion and were somewhat relieved when sitting down.

Examination.—A bulging above the clavicle and a movable mass, 8 cm. in diameter, over the left supraclavicular space were found on examination. Another firm immovable mass, 8 cm. in diameter, was seen over the inner third of the left clavicle. The lungs were clear and resonant, and the breathing was vesicular. There was a systolic murmur over the apex. The left arm could be raised only to a horizontal position, and there was limitation of rotation.

Laboratory Data.—Roentgen examination disclosed pathologic fracture of the left humerus, a large mass in the superior mediastinum, pathologic fracture of the neck of the left femur, areas of osseous destruction in the right innominate bone and in the shafts of the left tibia and fibula, extensive destruction and collapse of the body of the eleventh dorsal vertebra and partial destruction of the right half of the body of the tenth dorsal vertebra (fig. 10). Circumscribed areas of osseous destruction varying in size from that of a pinhead to about 1.5 cm. in diameter were noted in several ribs and in the skull. The urine was negative for albumin and Bence-Jones protein. Blood examination revealed 3,100,000 red cells, 4,800 white cells, 60 per cent hemoglobin, 65 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, 2 per cent eosinophils, 1 per cent monocytes and 2 per cent transitionals.

Course.—The patient received high voltage roentgen therapy over these regions and was discharged somewhat improved on November 4. She was readmitted to the hospital on Jan. 12, 1933, with pains in the lumbosacral region and in the lower extremities. On September 21 after an enema, the patient complained of a "break" in the back and girdle pains, with immediate loss of power in the lower extremities. Neurologic examination at this time disclosed marked tenderness over the tenth dorsal to the second lumbar vertebrae and a lesion at the level of the tenth dorsal segment, with complete flaccid paraplegia, absence of knee and ankle jerks, loss of all forms of sensation and retention of urine and feces. The patient died of bronchopneumonia on September 28. Autopsy was not performed.

Clinical Diagnosis.—The diagnosis was vertebral myeloma, with compression of the spinal cord and multiple myelomas.

Comment.—In this case there were destruction of the eleventh dorsal vertebra and collapse of its body with sudden compression of the spinal cord and its vessels, leading to neurologic signs and symptoms of a level lesion. The metastasis to the skull did not give rise to mental symptoms or neurologic signs.

Case 9.—H. D., a man aged 30, was admitted to the Montefiore Hospital on Feb. 25, 1930, with a history of pain in the left shoulder and in the chest since August 1929. After a spinal tap on January 17 he experienced complete loss of sensation below the nipples, stiffness and inability to move the legs, incontinence of urine and loss in sexual power. Laminectomy was done on January 20, between the second and the seventh dorsal segment. An extradural tumor was removed, which on histologic examination proved to be a myeloma. After laminectomy there was some return in sensation and in the motor power of the lower extremities. In October 1930 there was a recurrence of the girdle pains. The administration of high voltage roentgen therapy resulted in diminution of the pain and some return in sexual power.

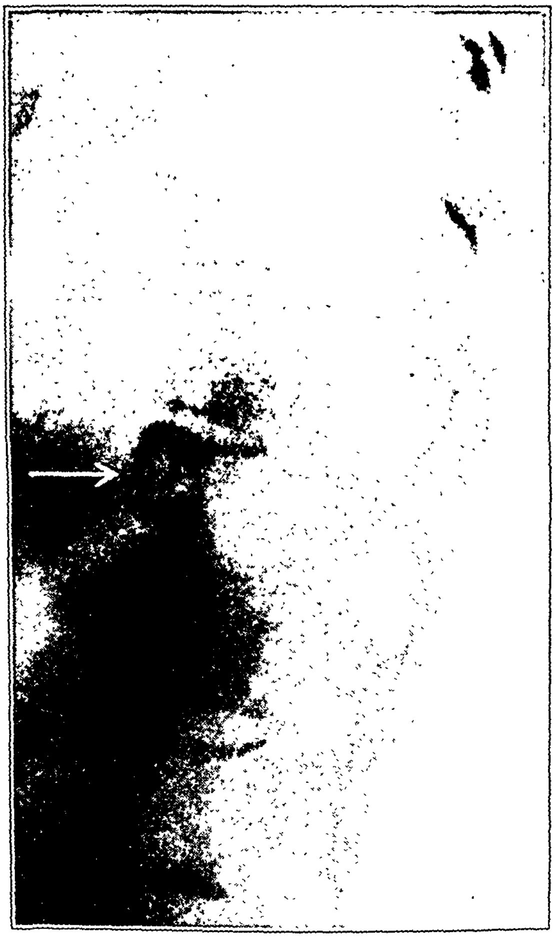

Fig. 10 (case 8).—Roentgenogram showing extensive destruction and collapse of the body of the eleventh dorsal vertebra and partial destrucrion of the body of the tenth dorsal vertebra.

Examination.—Physical examination revealed a limited expansion of the wall of the chest with all the sounds normal. Neurologic examination disclosed marked diminution in the motor power of the lower extremities, an increase in the deep reflexes, ankle clonus bilaterally, absence of abdominal and cremasteric reflexes and a positive Babinski toe sign and allied reflexes bilaterally. Pain, temperature and touch sense were impaired below the seventh dorsal segment; hypesthesia was less marked in the sacral region, vibration was lost from the knees down and position sense was impaired in the knees and ankles and lost in the toes There were also spontaneous flexion movements in one or the other limb, but never both, when the patient lay in bed quietly. There was diminution in libido and urinary retention.

Laboratory Data.—During the first admission roentgen examination of the dorsal region of the spine disclosed evidences of a laminectomy extending from the fourth to the tenth dorsal vertebrae, with partial collapse of the body of the sixth dorsal vertebra. There were also small circumscribed areas of osseous absorption in the left parietal region. The manometric readings disclosed a partial subarachnoid block with a positive globulin reaction and a total protein content of 25.3 mg. Examination of the blood revealed 75 per cent hemoglobin, 3,510,000 red cells, 8,600 white cells, 78 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes. The urine was negative for albumin and Bence-Jones protein.

Course.—The patient received further high voltage roentgen therapy, after which there was some return in sensation below the seventh dorsal segment. The spinothalamic sensory disturbances had disappeared, but the changes in the posterior column were still present. The patient was able to walk without assistance, although the gait remained spastic. The spontaneous flexion movements had also disappeard. The deep reflexes, however, remained unchanged. The patient was discharged as improved on December 26. He was again readmitted to the hospital on March 11, 1931, bcause of a pathologic fracture of the left arm. The neurologic condition remained unchanged. There was, in addition, herpes zoster over the right side of the thigh and of the abdomen, which cleared up under high voltage roentgen therapy. The patient became progressively worse and died of bronchopneumonia on July 24, 1931. Autopsy was not performed.

Clinical Diagnosis.—The diagnosis was multiple myeloma, with compression of the spinal cord.

Comment.—This case is of significance because of the sudden onset of a lesion at the level of the seventh dorsal segment after a spinal tap. In contrast to the second case, laminectomy and removal of the myeloma followed by high voltage roentgen therapy resulted in marked improvement of the neurologic signs.

CASE 10.—I. K., a man aged 60, was admitted to the Montefiore Hospital on Feb. 13, 1929, complaining of pain in the right hip and in the back since 1927. The pain came on in spasms and was most noticeable when the patient moved about but was absent when he was lying still. About five months later he was unable to stand because of weakness in the lower extremities. In January 1929 he complained of pain in the region of the sixth to the eighth dorsal vertebrae.

Examination.—Physical examination revealed a prominence between the eighth and the twelfth thoracic vertebra, marked tenderness in this region and limitation of motion. There was an area of dulness, with diminished breath sounds over the lower level of the left scapula. The liver was palpable 2 cm. below the costal margin. Neurologic examination revealed pain over the lumbosacral region. All the deep reflexes were hyperactive but equal. A questionable hypalgesia was found in the third, fourth and fifth right sacral dermatomes. There were herpetic eruptions from the second lumbar to the fifth sacral segments on the right.

Laboratory Data.—Roentgen examination disclosed destruction and partial collapse of the body of the eleventh dorsal vertebra (fig. 11). There were a few small areas of osseous absorption in the parietal, occipital and temporal regions of the skull. The red cell count ranged between 3,500,000 and 2,100,000; the hemoglobin content, from 70 to 40 per cent; the white cell count, from 4,800 to 2,600, with 28 per cent polymorphonuclear leukocytes, 48 per cent lymphocytes and 24 per cent myelocytes. The urine was positive for albumin and Bence-Jones protein.

Course.—The patient received high voltage roentgen therapy, with slight improvement in the symptoms. Later the axillary glands became enlarged. Death occurred on May 15. Autopsy was not performed.

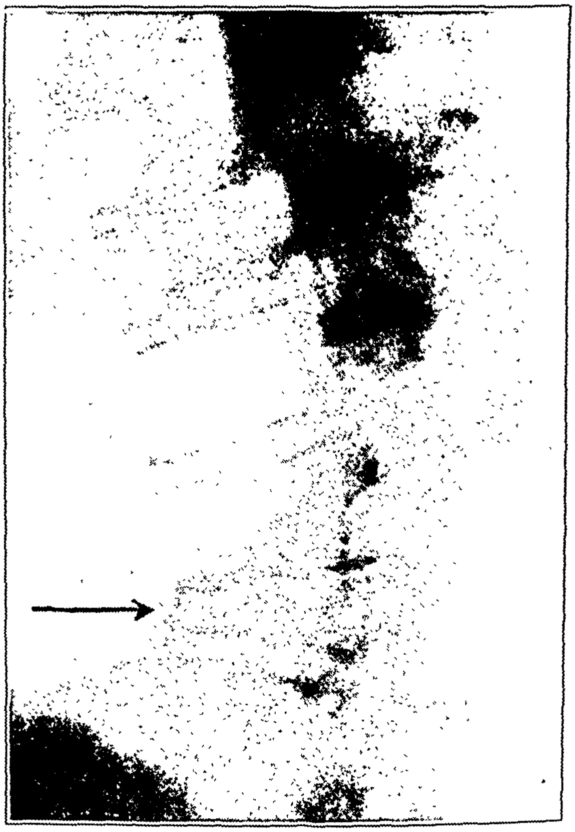

Fig. 11 (case 10).—Roentgenogram showing destruction and partial collapse of the eleventh dorsal vertebra.

Clinical Diagnosis.—The diagnosis was multiple myeloma and herpes zoster.

Comment.—In this case there was involvement of the skull and the lower dorsal vertebrae, as disclosed by roentgen examination. The neurologic signs consisted essentially of root pains and herpes zoster along the distribution of the second to the fifth sacral roots.

CASE 11.—H. A., a man aged 43, was admitted to the Montefiore Hospital on March 19, 1929, with a history of excruciating pains in the left lower anterior part of the chest radiating to the regions of the scapula, back and neck since October 1928. The pains would be relieved when he was sitting or lying quietly.

Examination.—Physical examination disclosed tenderness on pressure of the anterior part of the chest at the level of the sixth and seventh ribs. There was a soft systolic murmur at the apex. The neurologic examination, except for a generalized hyperreflexia, gave negative results.

Laboratory Data.—Roentgen examination disclosed multiple areas of osseous absorption scattered throughout all the bones of the skull, the seventh left rib and in both ilia; a partial collapse of the bodies of the seventh, eighth and twelfth dorsal vertebrae, and sclerosis of the bone in the lower lumbar vertebrae. Examination of the blood showed 2,560,000 red cells and 6,400 white cells, with 48 per cent hemoglobin, 62 per cent polymorphonuclear leukocytes, 26 per cent lymphocytes, 8 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The urine contained granular casts and white blood cells and was positive for albumin and Bence-Jones protein.

Course.—The patient became weaker, until he was hardly able to walk. He complained of constant throbbing headaches and sticking sensations over the upper left and right sides of the chest anteriorly, the lower extremities and the left arm. A small amount of high voltage roentgen therapy was administered, but owing to the critical condition of the patient it had to be discontinued. Twitching movements and uremic manifestations developed, with death on May 12.

Clinical Diagnosis.—The diagnosis was multiple myeloma.

Autopsy.—Gross Examination: Some of the ribs were thickened and infiltrated by metastases. Sections through the lower part of the spine and other bones showed irregularly grayish discoloration in the medullary tissue. The brain and spinal cord were not removed.

Microscopic Examination: The growth proved to be a myeloma.

Comment.—The inability to walk, the hyperreflexia, the sticking sensations over the chest, the twitching movements and the throbbing headaches were undoubtedly caused by the myeloma compressing the brain, spinal cord and roots. The localization of nodules within the skull and vertebrae, as shown by roentgen examination, confirms this opinion, although the brain and spinal cord were not removed at autopsy.

Case 12.—G. C., a woman aged 55, was admitted to the Montefiore Hospital on Oct. 12, 1928, complaining of weakness in the lower extremities, inability to walk and pains in the left arm, shoulders, hips and thighs since January 1928.

Examination.—There was extreme tenderness of the long bones on the left side and of the left ribs on movement or pressure. There was dulness on percussion of the chest, and râles were heard at the base posteriorly. A loud high pitched systolic murmur was audible over the precordium. The neurologic examination disclosed only absence of knee jerks.

Laboratory Data.—Roentgen examination disclosed bony destruction of the fourth, sixth, seventh and eighth ribs on the right side and of the seventh and eleventh ribs on the left side. The left shoulder and humerus contained large circumscribed areas of osseous destruction with a pathologic fracture through the lower third of the humerus. Similar areas of destruction were noted in the pelvic bones, the trochanters and the upper end of the shafts of both femurs. Numerous small circumscribed areas of osseous destruction of varying size were noted in all bones of the skull. Examination of the blood revealed 3,340,000 red cells, 50 per cent hemoglobin, 9,800 white cells, 55 per cent polymorphonuclear leuko[illegible] and 4 per cent myelocytes, with anisocytosis, poikilocy[illegible]. The urine was positive for albumin and Bence-Jon[illegible]

Course.—Th[illegible] voltage roentgen therapy, with some improvement. Later th[illegible]ed in the right parietal and in the right temporofrontal [illegible]stration of high voltage roentgen therapy resulted in some [illegible]. However, the patient became progressively worse and died [illegible]. A postmortem examination was not performed.

Clinical Diagn[illegible] was multiple myeloma.

Comment.—Th[illegible] signs, except for the absence of knee jerks, were negative. [illegible] inability to walk was most likely due to the numerous tumor nodules in the bones of the lower extremities.

COMMENT

In the first 3 cases in the series there were signs and symptoms of a level lesion. These were caused by compression of the vessels of the spinal cord by the diseased or fractured vertebrae. In the first case there was direct compression of the anterior spinal artery by a metastatic myeloma to the spinal dura. Direct myelomatous implantations in the spinal dura, as far as we know, have not been reported in the literature. In cases 2 and 3, and possibly in case 4, the diseased vertebrae compressed the dura and the vessels of the spinal cord. In both instances, the dura under the influence of the compressing agent, became extensively thickened and in addition to the diseased vertebrae acted as a factor in compressing the spinal cord. As in most of the cases recorded in the literature, the thoracic portion of the spinal cord was the usual site of compression; in the first case the midthoracic region was involved, and in the second and third cases, the lower thoracic region. The lumbar vertebrae were also implicated in cases 3 and 4. Spinal subarachnoid block was not noted in any of these cases. The root pains can easily be explained on the basis of direct compression of the posterior roots. In contrast to the cases recorded by Jacox and Kahn,[3] Klemme[4] and Denker and Brock,[5] and the eighth case in our series, improvement did not occur in our second case after laminectomy. High voltage roentgen therapy, however, gave some relief. Involvement of a single vertebra was not found in any of our cases. Myelomatous invasion of the vertebral column only with destruction of several vertebrae was noted in cases 1 and 2.

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[3] Jacox, H. W., and Kahn, E. A.: Multiple Myeloma with Spinal Cord Involvement, Am. J. Roentgenol. **30**:201, 1933.

[4] Klemme, R. M.: Plasma-Cell Myelomas Causing Cord Compression: Report of Five Cases, South. M. J. **26**:692, 1933.

[5] Denker, P. G., and Brock, S.: The Generalized and Vertebral Forms of Myeloma: Their Cerebral and Spinal Complications, Brain **57**:291, 1934.

In the entire group of cases of neural complications with involvement, the outstanding clinical findings consisted of vertebral tenderness, severe pain which was relieved when the were lying down (cases 5, 10 and 11), the presence of compr the cord (cases 1, 2, 3, 8, 9 and 11), compression of the roots in herpes zoster (cases 5, 9 and 10) and psychosis (case 5). 6 the peripheral neuritis of the upper extremities may have bee compression of the brachial plexus, to the severe secondary a to other unknown toxic factors. Peripheral neuritis in cases loma, as far as is known, was not recorded by other observ case 5, in spite of vertebral involvement, signs or symptoms pression of the cord were absent, and in case 7, although the were destroyed, the only neurologic sign elicited was ankle clon

The fifth case is of special interest because of the marked with a paranoid trend. Whether this was caused by the s anemia or by the compression of the cerebral structures by the m nodules in the cerebral dura and skull is difficult to state. It known that psychoses are observed in cases of pernicious and o secondary anemia. The mental symptoms in this case, however, the severe secondary anemia by one year. We are inclined to that the psychosis was the expression of an organic lesion cerebral circulatory dysfunction, as shown by the ischemic an pathologic changes of the nerve cells. The circulatory dysfunct the result of compression of the cerebral vessels by the myel nodules in the cerebral dura and skull. The patients in cases 4 had headaches, possibly due to the metastatic nodules to the s dura. In case 11 the twitching movements were most likely cerebral compression. Neurologic signs, such as convulsions an dipsia, as a result of involvement of the skull, were encountere first case reported by Denker and Brock.[5] Aronsohn [6] described insipidus in a case of multiple myeloma of the bones of the base skull.

The group of cases in which the brains and cords were not also presented interesting features. In contrast to case 2, the sy referable to the spinal cord in case 9 showed marked improveme laminectomy. The additional administration of high voltage r therapy cleared up almost all of the symptoms. This was the on in this group in which there was a partial subarachnoid block. last group there were 3 cases with slight neural complications (ca 11 and 12), and we wondered whether they were caused by comp of the cord. This is true of such findings as weakness of the extremities in case 10, the generalized hyperreflexia in cases 10 and 11 and the absence of knee jerks in case 12.

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[6] Aronsohn, H. G.: Zur pathologischen Anatomie und Symptom der multiplen Myelome, Virchows Arch. f. path. Anat. 281:78, 1931.

The symptoms referable to the spinal cord in cases of myeloma are most likely due to compression of the vessels of the spinal cord by the tumor or fractured vertebrae, leading to a myelopathic process. Direct compression of the spinal cord by the neoplasm, although less frequently observed, is another possibility. Nonne,[7] Kreuzer[8] and others expressed the belief that the neurologic signs are produced by the action of a toxin liberated by the neighboring myeloma. Nonne[7] came to this conclusion because he found the diseased vertebrae slightly lower than the supposedly compressed segments and because microscopic examination did not reveal any demonstrable lesion of the cord. Kreuzer,[8] in 1 case, found multiple areas of degeneration in the dorsolateral tracts of the cord, most marked in the ninth and tenth thoracic segments, although the fourth and fifth thoracic vertebrae were implicated. He therefore concluded that the symptoms referable to the spinal cord were not caused by mechanical pressure but by distant effects of the toxins. If this theory is correct, it is to be expected that in cases of myeloma signs referable to the spinal cord should be encountered more frequently distally instead of at the site of the diseased vertebrae. A survey of our cases and of others recorded in the literature proves, however, the contrary. As shown by Keschner and one of us (Davison),[9] the degree of compression of the spinal vessels by extradural neoplasm or agents varies, depending on the location and size of the compressing agent. The resulting myelopathic process at the level of compression will be slight, moderate or marked, depending on the foregoing factors as well as on the length of time of compression. Our cases of myeloma illustrate this. In the first case, although there was direct metastases to the spinal dura, because of the short duration of the pressure exerted the changes in the spinal cord were insignificant. The so-called influence of liberated toxins on the nervous system from this or other neoplastic diseases is undoubtedly emphasized too much.

It is to be stressed that the vertebral form of the disease occurs most frequently. In contrast to the 3 cases reported by Denker and Brock,[5] in none of our cases was there involvement of a single vertebra.

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[7] Nonne, M.: Zur Klinik der Myelomerkrankung der Wirbelsäule, Neurol. Centralbl. **40**:1, 1921.

[8] Kreuzer, H.: Plasmazelluläres Myelom mit multipler teilweise haemorrhagischer Herdmyelose der Medulla spinalis, Deutsche Ztschr. f. Nervenh. **90**: 224, 1926.

[9] Keschner, M., and Davison, C.: Myelitic and Myelopathic Lesions: V. Compression of the Spinal Cord by Expanding Lesions Producing Mild, Moderate or Marked Interference with the Circulation Leading to Myelopathy, Arch. Neurol. & Psychiat. **30**:592 (Sept.) 1933.

In cases 1 and 2, however, several vertebrae were diseased without other skeletal involvement.

Our material is of interest from other clinical angles. Most of our cases conform to Geschickter and Copeland's [10] dictum of the cardinal symptoms and signs in the diagnosis of multiple myeloma: (*a*) multiple involvement of the skeletal trunk, (*b*) pathologic fractures, (*c*) Bence-Jones proteinuria in from 65 to 70 per cent of the cases, (*d*) characteristic backache with early signs of paraplegia, (*e*) inexplicable anemia and (*f*) chronic nephritis, retention of nitrogen and hypertension. The symptoms and signs referable to vertebral involvement were amply discussed. It would be advisable to comment briefly on the other symptoms and signs.

An interesting feature is the age incidence. In 8 patients the disease appeared in the fifth and sixth decades and in 2 in the seventh and eighth decades (cases 3 and 7). Of unusual interest is the occurrence of the disorder in the patient in case 9 at the age of 29 and in the patient in case 4 at the age of 32. In Geschickter and Copeland's series,[10] 5 patients were under 35 years of age. There were 8 males and 3 females in our series. This is in accordance with the general view that the disease occurs twice as often in males as in females. The duration of the disease in our series varied between six months and sixteen years. It lasted a year or less in cases 1, 2, 3, 5, 7, 11 and 12; two years in cases 9 and 10; three years in case 6; nine years in case 8, and sixteen years in case 4. The duration of the illness over a period of sixteen years is the longest ever recorded in the literature. Slavens [11] reported a usual duration of about two years with a hopeless prognosis. As will be demonstrated, life can be prolonged by the administration of high voltage roentgen rays.

The Bence-Jones protein was positive in 5 of our cases. In the first 2 cases the test was not performed. The percentage of positive Bence-Jones protein in the urine in our cases is slightly lower than that in the case of Geschickter and Copeland,[10] who found it present in 65 per cent of their series, and much lower than in the cases of Magnus-Levy,[12] who found it positive in 80 per cent of his series. The percentage in our series might have been higher had the test been performed in the first 2 cases.

Severe secondary anemia was present in cases 2, 4, 5, 6, 7, 10 and 11 and moderate secondary anemia in cases 8, 9 and 12. Pathologic fractures were noted in most of our cases. Nephrosis, frequently reported in this disorder, was found in 10 of our cases.

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[10] Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1931.

[11] Slavens, J. J.: Multiple Myeloma in a Child, Am. J. Dis. Child. **47**:821 (April) 1934.

[12] Magnus-Levy, A.: Ueber die Myelomkrankheit, Ztschr. f. klin. Med. **121**:533, 1932.

Seven patients received high voltage roentgen treatment. In 4 there occurred slight improvement (cases 2, 4, 8 and 10), in 2 marked improvement (cases 9 and 11) and in 1 no improvement (case 5). The patients in cases 1, 3, 6, 7 and 12 did not receive deep high voltage roentgen therapy. Of the symptoms, pain was most frequently relieved by this type of therapy. The improvement in our cases after this treatment corresponds to that recorded by others and at present remains the best form of therapy. Jacox and Kahn[3] reported 2 cases in which excellent results followed laminectomy and roentgen therapy, 1 patient doing well five and one-half years after the onset of the symptoms. Wakeley's[13] patient was doing well for four and one-half years, and Coley's[14] patient remained well nine years and was still alive in 1931 after the same form of treatment. The condition in case 2 became worse after laminectomy but showed definite improvement after high voltage roentgen therapy. In the presence of metastases to the spinal cord with signs of compression of the cord, it is advisable to precede the administration of high voltage irradiation by laminectomy.

CONCLUSIONS

Twelve cases of multiple myeloma are reported. In 6 of these in which autopsy was performed, involvement of the spinal cord, roots, peripheral nerves or brain was found. In 6 cases with signs of lesions of the spinal cord or roots, the neural structures were not removed.

In most of the patients with lesions of the spinal cord the neurologic symptoms were produced by compression of the vessels of the spinal cord. A myelopathic process resulted from interference with the circulation. The damage to the fiber tracts depended on the degree and duration of the compression. In case 1 there was a direct metastasis to the spinal dura. Such lesions were, as far as we know, never described before.

The herpes zoster noted in a number of these cases was caused by the direct compression of the spinal roots by the neoplasm. In case 6 the peripheral neuritis may have been due to compression of the brachial plexus, severe anemia or unknown toxic factors.

In case 5 the myelomatous nodules of the cerebral dura and skull resulted in interference with the cerebral circulation and the production of a paranoid psychosis.

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[13] Wakeley, C. P. G.: Plasma-Celled Myelomatosis, Proc. Roy. Soc. Med. **25**:150, 1931.

[14] Coley, W. B.: Multiple Myeloma, Ann. Surg. **93**:77, 1931.

EXPERIMENTAL PRODUCTION OF GOITER

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Numerous attempts have been made by various investigators to produce goiter experimentally in animals. In a review of the literature it is striking that there are so many diverse experimental solutions of a problem about which so little is known. In many instances the observer was too anxious to note hyperplasia of the thyroid gland, and possibly because of enthusiasm alone he found it. Moreover, the question of control for such experiments repeatedly arises. Were they adequately controlled? It does not seem sufficient, especially in endemic goiter regions, to have the thyroid gland of a dog examined grossly and microscopically for the first time at the end of the period that a trial stimulus has been applied and to pronounce it hyperplastic by comparing it with a gland from an entirely different dog. Because of the great number of the experimental methods that have been reported as successful in the production of hyperplastic changes in the thyroid gland, it is almost impossible to eliminate all except one possible factor in one type of experiment. However, in any one type of experiment the results must be most carefully compared with the normal and, if possible, with a basic normal in the same animal.

The present report is based on experiments performed in an attempt to produce goiter in dogs and in guinea-pigs. In the experiments on dogs an attempt was made to insure a most rigid control by the following procedure:[1] At a preliminary operation the thyroid gland of each dog was measured, and a small piece, 2 by 2 mm., was removed from one of the lobes, usually the right. Subsequently, observations at operation or at necropsy were made, and a similar specimen was removed which was compared with the section obtained at the preliminary operation. In this manner each dog was self-controlled, although there were other controls from which sections were taken but in which no unusual stimulus was applied.

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[1] Mahorner, H. R.: Attempts to Produce Hyperplasia in Thyroid by Destruction of Part of Adrenals and by Infection, Proc. Soc. Exper. Biol. & Med. **29**:1076, 1932; Attempts to Produce Hyperplasia of Thyroid Gland by Infection and by Injury to the Adrenal Gland, ibid. **30**:770, 1933.

It is not desirable or feasible to review in detail all the literature pertaining to attempts to produce artificially hyperactivity or hyperplasia of the thyroid gland, but a few articles are cited to show a basis for some of my experiments.

Halsted[2] (1888) concluded from his microscopic studies of the thyroid glands of dogs suffering from low grade peritonitis induced by the intraperitoneal injection of a culture of staphylococci that infection causes hyperplastic changes in the thyroid gland. Womack and Cole[3] reported microscopic changes considered indicative of hyperplasia in the thyroid glands of dogs after implanting infected foreign bodies in the muscles of the necks of the animals. Plummer and Mayo[4] observed clinical hyperthyroidism in certain instances after the onset of an infectious process and expressed the belief that the infection precipitated the hyperthyroidism. McCarrison,[5] working in India, came to the conclusion that goiter is a filth-borne disease. Among numerous other experimental results, he reported[6] enlargement of the thyroid glands of rats kept under insanitary conditions.

According to Hellwig,[7] the theory that a high calcium intake might be responsible for the production of goiter is over one hundred years old, Waller[8] in 1912 suggested that hard water is the responsible factor in the production of goiter. Hellwig,[7] Hibbard[9] and others reported that a high calcium intake caused an increase in the size of the thyroid glands of animals. Bircher[10] in 1914, in experimental work on rats, found enlargement of the thyroid glands of animals which imbibed water of certain municipalities, whereas this observation was not made in controls which were given water from other sources. Webster and Chesney[11] reported the occurrence of goiter in rabbits fed on a diet purely of cabbage.

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[2] Halsted, W. S.: Reconsideration of the Question of Experimental Hypertrophy of the Thyroid Gland and the Effect of Excision of This Organ on Other of the Ductless Glands, Am. J. M. Sc. **147**:56, 1914.

[3] Womack, N. A., and Cole, W. H.: Normal and Pathologic Repair in the Thyroid Gland, Arch. Surg. **23**:466 (Sept.) 1931.

[4] Plummer, W. A., and Mayo, C. H.: Surgical Operations and Associated Infections as Possible Etiologic Factors in the Development of Exophthalmic Goiter, Surg., Gynec. & Obst. **53**:721, 1931.

[5] McCarrison, Robert: The Etiology of Endemic Goiter, Milroy Lectures, London, John Bale, Sons & Danielsson, 1913.

[6] McCarrison, Robert: Interaction of Food and Sanitary Condition in Causation of Thyroid Disease, Indian J. M. Research **20**:957, 1933.

[7] Hellwig, C. A.: Morphogeographic and Experimental Studies on Etiology of Goiter, West. J. Surg. **41**:453, 1933.

[8] Waller, H. E.: The Relationship of the Thyroid Gland to Other Internal Secretions of Sexual Origin, Practitioner **89**:279, 1912.

[9] Hibbard, J. S.: Experimental Thyroid Hyperplasia: Increased Intake of Chloride Combined with Diet Deficient in Iodine as a Factor, Arch. Surg. **26**: 648 (April) 1933.

[10] Bircher, E.: Das Kropfproblem, Beitr. z. klin. Chir. **89**:1, 1914.

Golyakowsky[12] in 1899 reported that ligation of the adrenal vessels resulted in elevation of the basal metabolic rate. The metabolic rate was said to decrease slowly after an initial rise within ten days followed by a subsequent elevation to plus 50 per cent between the second and the fourth week. A return of the basal metabolic rate to normal or below occurred in the sixth or seventh week. Marine and Baumann[13] in 1921, using rabbits, obtained a rise in the metabolic rate in 57 per cent of instances in which the adrenal glands were injured or removed. They found that dogs died within twenty-four hours after bilateral adrenalectomy, whereas rabbits were able to survive the procedure, probably because of accessory adrenal tissue in the latter. The increased metabolism continued for one, two or three weeks with or without slight remissions. Marine[14] in 1930 expressed the opinion that this experimental condition is similar to exophthalmic goiter.

The following authors, to cite only some of the many who have written reports on the subject, have presented evidence obtained from experiments on animals, either by measuring the metabolism or by histologic and chemical studies of the thyroid gland and its effect on metamorphosis in tadpoles and salamanders, that extracts from the anterior lobe of the pituitary body activate the thyroid gland, diminish the colloid content of the follicle, diminish the iodine content of the gland and elevate the basal metabolic rate: Smith and Smith,[15] Schwartzbach and Uhlenhuth,[16] Silberberg,[17] Uhlenhuth and Schwartzbach,[18] Loeb and

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[11] Webster, B., and Chesney, A. M.: Studies in the Etiology of Simple Goiter, Am. J. Path. **6**:275, 1930.

[12] Golyakowsky, cited by Marine and Baumann.[13]

[13] Marine, D., and Baumann, E. J.: Influence of Glands with Internal Secretion on Respiratory Exchange: Effect of Suprarenal Insufficiency (by Removal or by Freezing) in Rabbits, Am. J. Physiol. **57**:135, 1921.

[14] Marine, D.: Studies on Etiology of Goiter Including Graves' Disease, Ann. Int. Med. **4**:423, 1930.

[15] Smith, P. E., and Smith, I. P.: The Repair and Activation of the Thyroid in the Hypophysectomized Tadpole by the Parenteral Administration of Fresh Anterior Lobe of the Bovine Hypophysis, J. M. Research **43**:267, 1922.

[16] Schwartzbach, S. S., and Uhlenhuth, E.: Anterior Lobe Substance, the Thyroid Stimulator, Proc. Soc. Exper. Biol. & Med. **26**:153, 1928.

[17] Silberberg, M.: Effects of Combined Administration of Extracts of Anterior Lobe of Pituitary and Potassium Iodide on Thyroid Gland, Proc. Soc. Exper. Biol. & Med. **27**:166, 1929.

[18] Uhlenhuth, E., and Schwartzbach, S. S.: Anterior Lobe, the Thyroid Activator, Anat. Rec. **42**:41, 1929.

Bassett,[19] Aron,[20] Benedict, Putnam and Teel,[21] Siebert and Smith,[22] Janssen and Loeser,[23] Loeser,[24] Loeb and Friedman,[25] Schockaert,[26] Grant,[27] Verzár and Wahl,[28] Siebert and Thurston,[29] Closs, Loeb and MacKay,[30] Junkmann and Schoeller,[31] Thurston,[32] Anderson and Collip,[33] Greep,[34] Collip and Anderson,[35] Friedgood [36] and others.

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19. Loeb, L., and Bassett, R. B.: Effect of Hormone of Anterior Pituitary on Thyroid Gland in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **26**:860, 1929.

20. Aron, M.: Action de la préhypophyse sur le thyroïde chez le cobaye, Compt. rend. Soc. de biol. **102**:682 (Nov. 29) 1929; Particularites histologiques de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse, ibid. **103**:145 (Jan. 24) 1930.

21. Benedict, E. B.; Putnam, T. J., and Teel, H. M.: Early Changes Produced in Dogs by Injecting Sterile Active Extract from Anterior Lobe of Hypophysis, Am. J. M. Sc. **179**:489, 1930.

22. Siebert, W. J., and Smith, R. S.: The Effect of Various Anterior Pituitary Preparations upon Basal Metabolism in Partially Thyroidectomized and in Completely Thyroidectomized Guinea Pigs, Am. J. Physiol. **95**:396, 1930.

23. Janssen, S., and Loeser, A.: Die Wirkung des Hypophysenvorderlappens auf die Schilddrüse, Arch. f. exper. Path. u. Pharmakol. **163**:517, 1931.

24. Loeser, A.: Hypophysenvorderlappen und Jodgehalt der Schilddrüse, Arch. f. exper. Path. u. Pharmakol. **163**:530, 1931.

25. Loeb, L., and Friedman, H.: Long Continued Injections of Acid Extract of Anterior Pituitary on Thyroid Gland and Sex Organs, Proc. Soc. Exper. Biol. & Med. **29**:172, 1931.

26. Schockaert, J. A.: Hyperplasia of Thyroid and Exophthalmos from Treatment with Anterior Pituitary in Young Duck, Proc. Soc. Exper. Biol. & Med. **29**:306, 1931.

27. Grant, M. P.: The Release of Follicular Colloid from the Thyroid of Necturus Maculosus Following Heteroplastic Anterior-Pituitary Implants, Anat. Rec. **46**:373, 1930.

28. Verzár, F., and Wahl, W.: Wirkung der Hypophysenvorderlappen-hormons auf den O_2-Verbrauch von Meerschweinchen, Biochem. Ztschr. **240**:37, 1931.

29. Siebert, W. J., and Thurston, E. W.: Basal Metabolism After Potassium Iodide with Acid Extract of Anterior Pituitary Glands, Pituitary Tablets and with Thyroid, Proc. Soc. Exper. Biol. & Med. **29**:652, 1932.

30. Closs, K.; Loeb, L., and MacKay, E. M.: The Effect of an Acid Extract of the Anterior Pituitary on the Iodine Concentration of the Blood and Thyroid Gland, J. Biol. Chem. **96**:585, 1932.

31. Junkmann, K., and Schoeller, W.: Ueber das thyreotrope Hormon des Hypophysenvorderlappens, Klin. Wchnschr. **11**:1176 (July 9) 1932.

32. Thurston, E. W.: A Comparison of Hypertrophic Changes in Thyroid Caused in Different Species by Acid Extract of the Anterior Lobe of the Bovine Pituitary Gland, Arch. Path. **15**:67 (Jan.) 1933.

33. Anderson, E. M., and Collip, J. B.: Thyreotropic Hormone of Anterior Pituitary, Proc. Soc. Exper. Biol. & Med. **30**:680, 1933.

34. Greep, R.: Effect of Luteinizing and Follicular Stimulating Fractions of Pituitary on Thyroid, Proc. Soc. Exper. Biol. & Med. **30**:1362, 1933.

(Footnotes continued on next page)

The literature on the subject contains numerous reports of changes in the thyroid gland produced by other substances.[36a] Even the foregoing literature contains many conflicting reports. It could easily be shown that the substances which are said to be efficacious in producing changes in the thyroid gland are numerous and that the results reported by different authors are frequently so incongruous that doubt is cast on the reliability of both, and the weight of whichever one is correct is miscarried.

INFECTION AS A STIMULUS FOR THE PRODUCTION OF HYPERPLASIA IN THE THYROID GLAND

Fourteen dogs were used in an attempt to produce hyperplasia of the thyroid gland by means of infection. No attempt was made to produce a deficiency of iodine in the diet in this or in the other experiments. The fourteen dogs were divided into three groups, the first two consisting of four dogs each and the last of six dogs (table 1). At a preliminary operation the thyroid gland of each dog was exposed by a midline incision. The gland was measured, and a piece of tissue approximately 2 by 2 mm. was removed from the anterior border of the right lobe. This was sectioned and stained with hematoxylin and eosin for comparison as a microscopic control with subsequent sections. At the time of the first operation a contaminated foreign body was sewed into the right sternocleidomastoid muscle of the dog. A different contaminating culture was used in each group. In the first group (dogs 20, 21, 22 and 23) the foreign body was a small coil of silver wire contaminated with a pure culture of staphylococci. Each of these wounds remained infected throughout the experiment, and at the end of four, eight, sixteen and twenty-five days, respectively, the dogs were killed. The thyroid glands were measured again, and each was sectioned and stained with hematoxylin and eosin and compared with the section removed at the preliminary operation from the same dog. In no instance was there any definite change in the thyroid gland, either grossly or microscopically.

The experiment on the second group of dogs (53, 54, 55 and 56) was conducted in the same manner as that on the first group, except that the foreign body was a small piece of tape, approximately 0.5 by 0.5 cm., which was contaminated with a mixed culture of excrement obtained during colostomy on a human being. The dogs were killed after eight, seventeen, thirty-two and sixty-four days, respectively. The wound of the first three showed infection at the time the animal was killed. In the last dog the wound was healed. There were no appreciable gross or microscopic changes in any of the thyroid glands when the specimens obtained at necropsy were compared with those obtained at the preliminary operation.

There were six dogs (58, 59, 60, 61, 62 and 63) in the third group. The foreign body was tape contaminated with mixed anaerobic and aerobic cultures

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35. Collip, J. B., and Anderson, E. M.: The Production of Serum Inhibitory to the Thyrotropic Hormone, Lancet 1:76 (Jan. 13) 1934.

36. Friedgood, H. B.: Experimental Exophthalmos and Hyperthyroidism in Guinea-Pigs: Clinical Course and Pathology, Bull. Johns Hopkins Hosp. **54**:48, 1934.

36a. For a more detailed review see Mahorner, H. R.: Recent Advances in Surgery of the Thyroid Gland, Surgery **2**:280 (Aug.) 1937.

of excrement obtained at colostomy on a human being. The contaminated tape was sewed into the right sternocleidomastoid muscle at the preliminary operation, at which time the lobes of the thyroid gland were measured and a biopsy specimen was taken from the right lobe. The dogs were killed by electrocution at the end of nine, twenty, twenty-one, thirty and fifty days, respectively, and at the time

TABLE 1.—*Results of Implantation of Infected Foreign Bodies*

Dog No.	Initial Weight, Kg.	Method	Duration of Experiment, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
20	8.7	Implantation of silver wire contaminated with staphylococci into muscle of the neck	4	Infected wound	Hyperplasia (?)
21	9.1	Implantation of silver wire contaminated with staphylococci into muscle of the neck	8	Infected wound	No change
22	7.5	Implantation of silver wire contaminated with staphylococci into muscle of the neck	16	Infected wound	No change
23	7.7	Implantation of silver wire contaminated with staphylococci into muscle of the neck	25	Infected wound	No change
53	8.18	Implantation of tape contaminated with mixed culture into muscle of the neck	8	Infected wound	No change
54	11.7	Implantation of tape contaminated with mixed culture into muscle of the neck	17	Infected wound	No change
55	...	Implantation of tape contaminated with mixed culture into muscle of the neck	32	Infected wound	No change
56	...	Implantation of tape contaminated with mixed culture into muscle of the neck	64	Normal; wound healed	No change
59	9.8	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	9	Infected wound; culture showed mixed infection, bacilli and cocci	No change
62	9.6	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	20	Infected wound; culture showed mixed infection	No change
63	6.3	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	20	Infected wound; culture showed mixed infection	Retrogressive change
58	9.6	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	21	Infected wound; culture showed mixed infection	No change
60	7.6	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	30	Infected wound; culture showed mixed infection	No change
61	7.0	Implantation of anaerobic and aerobic culture from feces into muscle of the neck	50	Wound healed	No change

each animal was killed the right sternocleidomastoid muscle was explored aseptically and the region of the implanted foreign body located. An abscess was found in all dogs except the last. These abscesses were cultured, and in each instance a mixed culture of organisms was found. At necropsy the size of the thyroid gland was measured. Sections were made of each lobe, and these were stained with hematoxylin and eosin and compared with the section removed at the preliminary operation from the same dog. In no instance was there gross or microscopic evidence of change in the thyroid gland.

The results in these experiments support the conclusion that a focus of infection in the dog does not produce changes in the thyroid gland suggestive of hyperplasia, at least within a period of thirty-two days. Whereas these results do not prove definitely that infection is not a factor in the production of goiter, they do not corroborate the observations (that infection does produce hyperplasia of the thyroid gland) of other investigators whose similar experiments were less well controlled.

I have examined the thyroid glands of a number of other dogs (not included in this series) that died of infections and have never found microscopic evidence that the infection induced hyperplasia. It is true that by careful study one can pick out small individual areas in which the acini are small and have less colloid than other areas of the gland. The colloid may even appear slightly bluish, but this is not unmistakable evidence of hyperplasia, because similar areas can be found in sections from the thyroid glands of other normal control animals. Desquamation of cells into the acini was found in tissue which has undergone postmortem degeneration. Selected microscopic fields are not to be accepted as representative of the appearance throughout an entire section. Unmistakable evidence of diffuse histologic changes is presented in certain experiments reported herein by deliberately avoiding the fallacy of judging the appearance of a whole gland from that of one particular field. By care exerted to show widest discrepancies in microscopic fields and not the average appearance of the section, an author can demonstrate variations that suggest that microscopic changes have taken place when this is not actually true (figs. 1 and 2). Enthusiasm and eager credulousness may be responsible for an incorrect interpretation of small selected areas as evidence of hyperactivity of the thyroid gland. What is really desirable in such experiments is changes so striking that the evidence is incontestable.

DISTURBANCE OR DEFICIENCY IN THE ADRENAL GLANDS AS A STIMULUS FOR THE PRODUCTION OF HYPERPLASIA IN THE THYROID GLAND

Because of the repeatedly expressed opinions that the cause of hyperthyroidism is dysfunction of the adrenal gland and because of the experiments of Marine and Baumann[13] showing that an increase in the basal metabolic rate resulted from removal of part of the adrenal tissue or from freezing the adrenal glands, I attempted to repeat the experiments, using a different method to note the effect of adrenal "deficiency" on the thyroid gland. A section from the thyroid gland of an animal removed after injury to the adrenal gland, the interval after injury varying in different animals, was compared with a section removed at a preliminary operation. Marine and Baumann[13] stated that after decreasing the amount of adrenal tissue by removal in rabbits or after freezing the adrenal glands the basal metabolic rate was elevated. Marine[14] concluded from this that the elevation of the basal metabolic rate indicates true hyperthyroidism. Granting that the etiologic factor in hyperthyroidism originates outside the thyroid gland, it is safe to conclude that true hyperthyroidism will be attended by some evidence of hyperplasia in the thyroid gland albeit secondary to a stimulus outside the gland. Conversely, it is fair to assume that absence of hyperplasia under similar conditions in which there is elevation of the basal metabolic rate indicates that the elevated basal metabolic rate is not due to true hyperthyroidism.

Dogs were used for this experiment. At a preliminary operation the thyroid gland was exposed through a midline incision and measured. A piece of tissue, 2 by 2 mm., was removed from the anterior border of the right lobe. The wound was closed, and at a subsequent operation, after the wound had healed, the adrenal glands were exposed either through two lumbar incisions or through a midline abdominal incision. (The former was found to be more satisfactory.) The adrenal glands were crushed with a hemostat, and from one third to one half of one of the glands was left intact. The extent of this procedure is indicated in

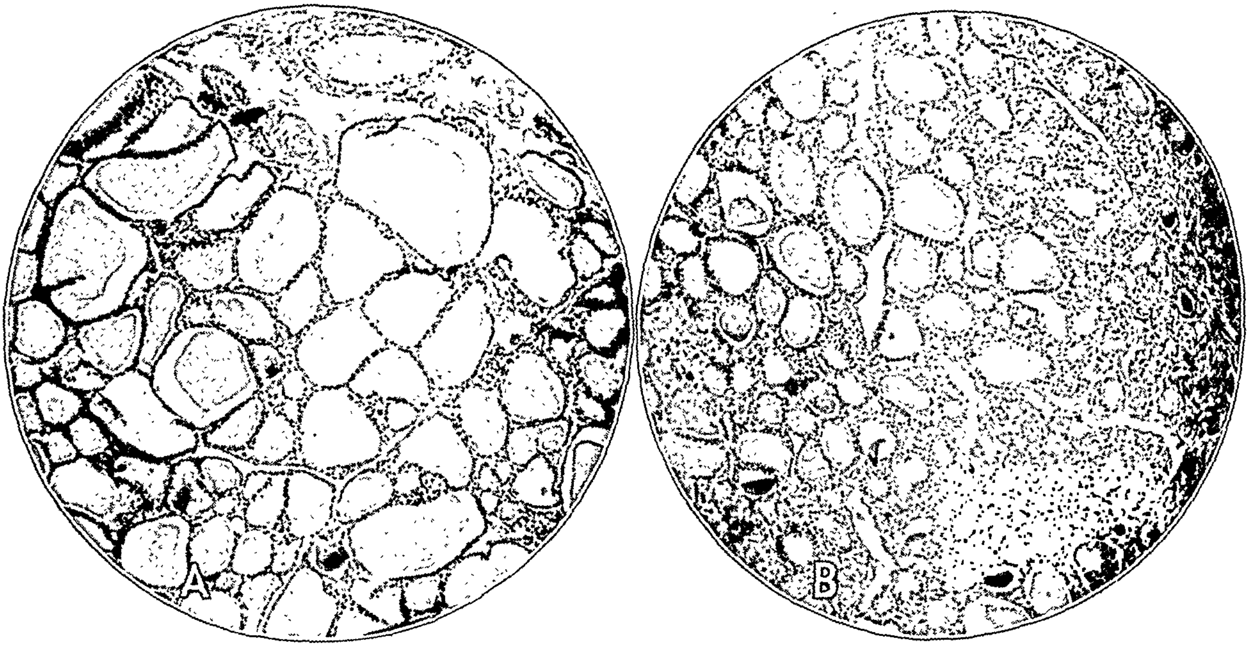

Fig. 1.—*A* and *B* are two different sections taken from the thyroid gland of a dog at the time after the animal had received 1 cc. of the gonadotropic principle of the urine of pregnant women daily for twelve days. There is more colloid and the acini are larger *in A than in B. Tiny vesicles may be seen in the colloid* in *B*, and the epithelial cells are more cuboidal, but this section is a selected area. There was no essential difference in the preliminary sections and the twelve day sections. This shows that erroneous results may be demonstrated by selecting foci not representative of the average in a section for photomicrography. The magnification of *A* and *B* is the same.

table 2. The wound was closed, and the animals either died or were killed in from five to one hundred and twenty-seven days. In the first ten days after the procedure the animals appeared sick, were apathetic and moved slowly, and several of them died. In some of the animals the systolic blood pressure fell from 180 to 80 mm. of mercury. Several of the animals died within the first few days after

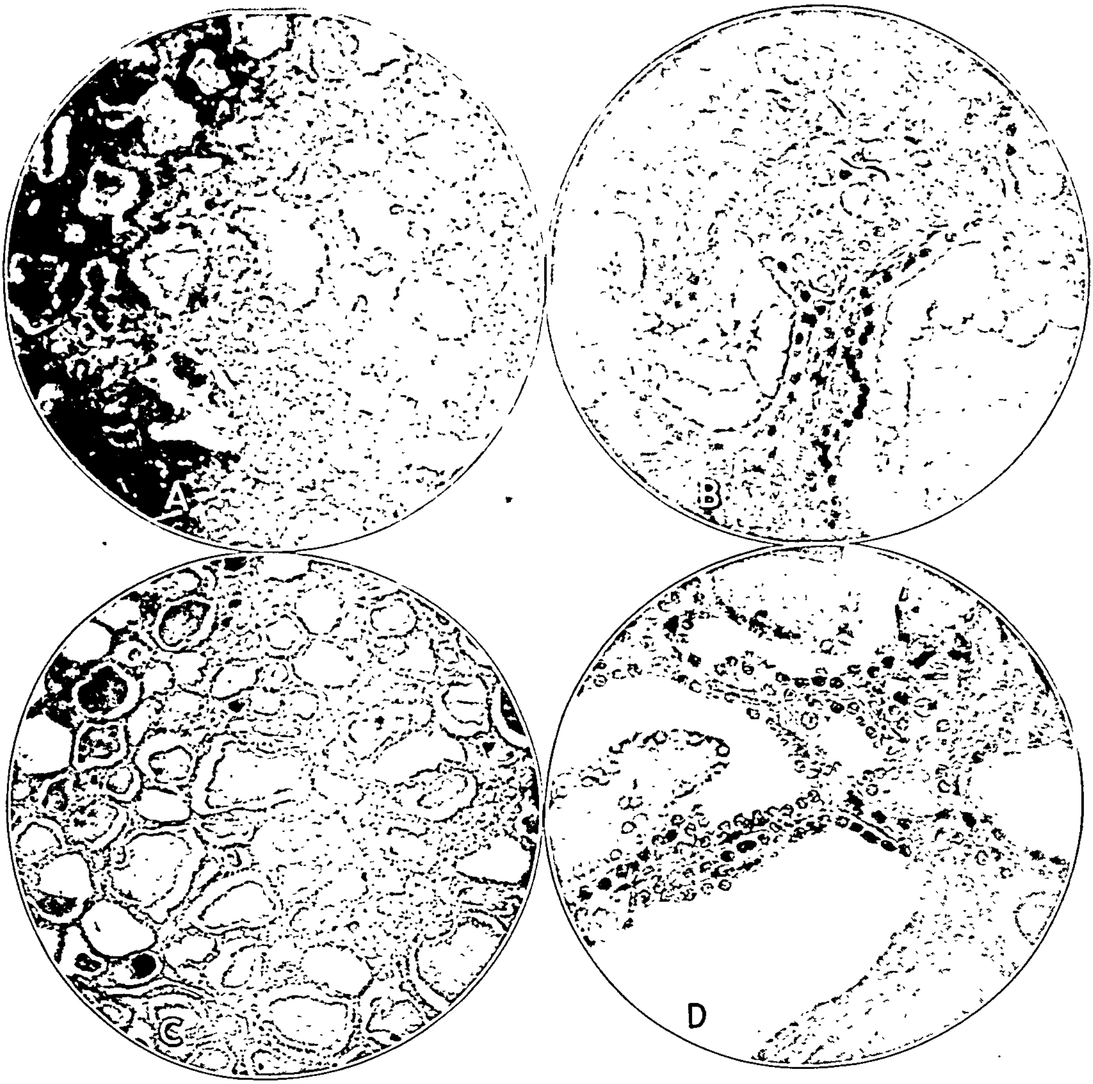

Fig. 2 (dog 61).—*A* and *B* are low and high power photomicrographs of sections of the thyroid gland before implantation of an infected foreign body into the muscles of the neck of a dog, and *C* and *D* are two corresponding magnifications of sections taken fifty days after implantation. Seeing *C* and *D* alone, one might suspect that the thyroid gland in this dog is more active than normal, but with the control there is no doubt that no histologic change has occurred. Note the tiny vesicles (supposed to be absorption vesicles) in the colloid in *C* and *D*.

the operation and are not considered in the report. Three died in from nine to eleven days. There was no suggestion of nervousness or excitability in the dogs. They looked apathetic and sluggish. Those that lived were killed individually in from five to one hundred and twenty-seven days by electrocution. A complete autopsy was done, and the thyroid and adrenal glands were measured and sectioned for microscopic examination. The adrenal glands of animals killed within two weeks showed the result of contusion; those of the animals killed later in some instances were smaller than normal, but in all the animals the wounds had healed. In three animals (6, 7 and 8) exploration was done to obtain a biopsy specimen from the thyroid gland between the time of operation on the adrenal gland and the date the animal was killed. Subsequent sections were obtained from the thyroid glands of twelve animals in the following periods after the operation on the adrenal glands: five, six, nine, ten, ten, eleven, eleven, fourteen, fourteen, twenty-four, twenty-four, one hundred and three, one hundred and seventeen and one hundred and twenty-seven days, respectively.

TABLE 2.—*Results of Crushing the Adrenal Glands*

Dog No.	Initial Weight, Kg.	Method	Interval After Injury to Adrenal Gland, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
24	13.7	Entire left and ⅔ of right adrenal gland crushed	5	Looked sick; moved slowly; moribund; killed	No change in thyroid
14	7.1	Entire left adrenal gland crushed	6	Thin; emaciated; looked sick; killed	No change in thyroid; left adrenal ⅔ macerated
25	13.8	Entire left and ⅔ of right adrenal gland crushed	9	Looked normal; killed	No change in thyroid; both adrenals partially destroyed
26	6.6	Entire left and ⅔ of right adrenal gland crushed	10	Sick; died	No change in thyroid; ½ right adrenal remained; no left adrenal
33	...	½ of right and entire left adrenal gland crushed	10	Sick; died	No change in thyroid
29	7.5	Entire right and ⅔ of left adrenal gland crushed	11	Emaciated; died	No change in thyroid; left adrenal ½ normal; right, ⅓ normal size
13	3.9	Entire right adrenal gland crushed	11	Healthy	No change in thyroid; right adrenal missing
8	8.2	Entire left and ⅓ of right adrenal gland crushed	14	Sick; moves slowly	No change in thyroid
8	8.2	....	103	Healthy	No change in thyroid; adrenals normal size
7	7.5	Entire right and ⅓ of left adrenal gland crushed	14	Sick; moves slowly	No change in thyroid
7	7.5	....	117	Healthy	No change in thyroid
5	7.1	Entire left and ¼ of right adrenal gland crushed	24	Weak; moves slowly	No change in thyroid; died; no cause found; regeneration of adrenals
6	6.4	Entire left adrenal gland crushed	24	Weak	No change in thyroid
6	6.4	....	127	Normal	No change in thyroid

Comparison of the gross measurements and histologic appearance of sections of thyroid gland obtained at the preliminary operation with subsequent sections from the same gland showed no evidence of hyperplasia or retrogression.

FREEZING THE ADRENAL GLANDS AS A STIMULUS TO THE PRODUCTION OF HYPERPLASIA IN THE THYROID GLAND

Seven dogs were used in an attempt to show whether freezing the adrenal glands would produce hyperplasia of the thyroid gland (table 3). At a preliminary operation the thyroid gland of each dog was measured, and a small piece of tissue, 2 by 2 mm., was removed from the right lobe. This was stained as a normal section with which to compare later sections. After the preliminary wound had healed, each adrenal gland was exposed by a lumbar incision and frozen solidly with a spray of ethyl chloride for several minutes. The wound was then closed. One animal died in four days as a result of this procedure. They were all sick, sluggish and apathetic and lost weight. The remaining animals were killed after thirteen, fourteen, nineteen, twenty-five, seventy-one and eighty-five days, respectively. The measurements and microscopic appearance of the thyroid glands were compared with those obtained at the preliminary operation. At necropsy the adrenal glands showed hemorrhage grossly and microscopically. Petechiae were still present in the adrenal glands of the animal killed twenty-five days after freezing. Moreover, in some instances the glands seemed to remain smaller than normal.

TABLE 3.—*Results of Freezing Adrenal Glands*

Dog No.	Initial Weight, Kg.	Method	Interval After Freezing Adrenal, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
47	4.9	Both adrenal glands frozen	4	Sick; died	No change in thyroid; adrenals hemorrhagic
82	9.4	Both adrenal glands frozen	13	Sick, sluggish and emaciated; killed	No change in thyroid; left adrenal infected
45	7.4	Both adrenal glands frozen	14	Normal	No change in thyroid; adrenals ⅓ normal size
81	7.0	Both adrenal glands frozen	19	Normal	No change in thyroid; petechiae in right adrenal; hyaline degeneration in left
46	6.8	Both adrenal glands frozen	25	Emaciated; sluggish	No change in thyroid; left adrenal showed petechiae
44	5.5	Both adrenal glands frozen	71	Thin; apathetic	No change in thyroid; left adrenal normal; right adrenal ⅓ normal size
43	5.6	Both adrenal glands frozen	85	Normal	No change in thyroid; adrenals slightly smaller than normal

In no instance was there gross or microscopic evidence of hyperplasia or retrogression of the thyroid gland.

HIGH CALCIUM CHLORIDE INTAKE AS A STIMULUS FOR THE PRODUCTION OF HYPERPLASIA IN THE THYROID GLAND

Six dogs were used in experiments on the effect of a high calcium chloride intake on the thyroid gland (table 4). At a preliminary operation the thyroid gland of each dog was measured, and a small piece of the right lobe, 2 by 2 mm., was removed for microscopic study. Four animals were given 2 per cent calcium chloride in distilled water. They refused to drink this concentrated solution, and after five days they were given 500 cc. of the solution twice daily, by stomach tube. Because all of the dogs suffered from continued vomiting after four days of this regimen and after one of the dogs (65) died, 0.05 per cent calcium chloride in distilled water was used as drinking water for the remainder of the experiment. Two other dogs (68 and 69) were started on this solution as their only drinking water immediately after the preliminary operation. Four of the six dogs died after six, seven, twelve and ninety-six days, respectively. The remaining two were killed after drinking the calcium water for eight and one hundred and thirteen days, respectively. At necropsy the thyroid gland of each animal was measured. Sections stained with hematoxylin and eosin were compared with the original sections removed at the preliminary operation.

TABLE 4.—*Results with a High Calcium Intake*

Dog No.	Initial Weight, Gm.	Method	Duration of Experiment, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
68	*3.8*	*Calcium chloride 0.05%*	*6*	*Died*	*Hyperplasia (?)*
65	7.8	Calcium chloride 2%, 500 cc. daily	7	Sick; died	Smaller acini; less colloid
66	10.2	Calcium chloride 2%, 500 cc. daily	12	Sick; died	No change
69	6.6	Calcium chloride 0.05%	80	Healthy	Definite hyperplasia
64	10.3	Calcium chloride 2%, 500 cc. daily for 8 days and 0.05% for 88 days	96	Sick; died	Hyperplasia (?); postmortem degeneration
67	10.1	Calcium chloride 2% for 8 days and 0.05% for 105 days	113	Healthy	Definite hyperplasia

TABLE 5.—*Blood Calcium Determinations on Dogs Drinking Calcium Water*

Dog No.	Preliminary Estimation of Blood Calcium, Mg. High	Low	Date of Starting Experiment	Subsequent Calcium Determinations, Mg.
68	10.12	10.06	July 17	July 23, death
65	*10.78*	*10.62*	*June 14*	*June 15, 10.52*; June 20, 11.01; June 22, death
66	11.19	10.92	June 14	June 15, 11.48; June 20, 11.21; June 26, death
69	11.42	11.42	July 17	July 27, 10.98; August 2, 11.14; August 9, 12.78; August 16, 11.48; August 23, 12.49; August 30, 14.20; September 6, 11.32; September 13, 12.03; September 20, 10.92; September 27, 11.46; October 4, 12.33; October 5, killed
64	*10.90*	*10.51*	June 14	June 15, 11.58; June 21, 11.96; June 27, 11.14; July 3, 11.14; July 10, 11.14; July 27, 10.51; August 2, 11.14; August 9, 12.78; August 16, *9.64*; August 23, 9.49; August 30, 10.12; September 6, 8.82; September 13, 8.69; September 17, necropsy
67	*11.33*	*10.90*	June 14	June 15, 11.2; June 20, 14.61; June 27, 11.28; July 3, 11.28; July 10, 11.14; July 27, 10.51; August 2, 11.14; August 9, 12.78; August 16, 11.64; August 23, 12.25; August 30, 11.70; September 6, 10.17; September 13, 11.23; September 20, 10.92; September 27, 10.26; October 4, 10.64; October 5, killed

Prior to initiating the experiment, determinations were made on the blood calcium in each dog on at least two different days. During the course of the experiment, while the dogs were taking the calcium solution, determinations were made on the blood calcium once a week. The calcium content of the blood was elevated from 0.5 to 2 mg. by the inhibition of calcium chloride drinking water, but as may be seen from table 5 the elevation was not constant. Determinations were made after the food was removed from the cages over night and the dogs were permitted to drink calcium chloride water.

Gross measurements of each gland showed no appreciable difference between the measurements made at necropsy and those made at the preliminary operation, but microscopically the changes were striking (fig. 3), not only in isolated or selected areas but throughout the gland. There was evidence of hyperactivity as indicated by less colloid in the vesicles, even to complete disappearance; large columnar epithelium, and marked vesicular changes in the colloid, not only at the periphery but throughout the entire acini, so that the colloid looked as if it had degenerated into bubbles. No changes were found in the thyroid glands of dogs dying after seven and twelve days, respectively. There were questionable changes in the thyroid gland in the dog that died after six days, and definite changes in the glands of dogs that died after eighty, ninety-six and one hundred and thirteen days.

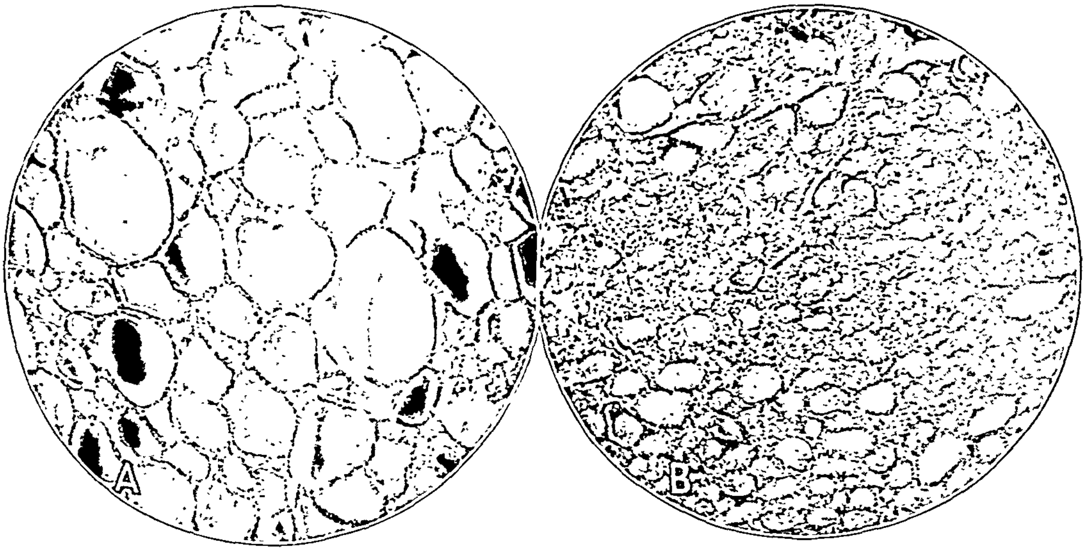

Fig. 3 (dog 67).—*A* is a preliminary section from the thyroid gland of a dog. *B* is a section from the thyroid of the same dog taken one hundred and thirteen days later, after drinking 0.05 per cent calcium chloride water during that interval. The magnification is the same as that of *A*. The entire microscopic appearance has changed. From flat epithelium lining the acini in *A*, the epithelium has changed to a more cuboidal form in *B* but seems in some instances to be several layers thick. The acini are smaller in *B*, and numerous tiny vesicles are found throughout the colloid. These are representative of the entire section and are not selective areas.

These experiments indicate that calcium eliminates the colloid from the thyroid gland and increases the size of the epithelium. Thus, from these experimental results, at least, it does not seem that calcium chloride is the cause of colloid goiter but that it does change the histologic appearance of the thyroid gland.

GONADOTROPIC PRINCIPLE FROM THE URINE OF PREGNANT WOMEN AS A STIMULUS TO PRODUCTION OF HYPERPLASIA OF THE THYROID GLAND

Five dogs were used to determine the effect of the gonadotropic principle from the urine of pregnant women on the thyroid gland. At a preliminary operation the thyroid gland of each dog was exposed and measured, and a piece of tissue, 2 by 2 mm., was removed from the right lobe and sectioned to serve as a normal section for comparison. Thereafter, 1 cc. of the gonadotropic principle[37] was injected intraperitoneally daily for the remainder of the experiment. The remaining dogs were killed in six, eleven, twelve, twenty-five and fifty-one days, respectively. At necropsy the thyroid gland of each animal was removed, measured and sectioned. The material was stained with hematoxylin and eosin and compared with the section removed at the preliminary operation from the same dog.

In none of the dogs was there any gross or microscopic evidence of hyperplasia or changes in the thyroid gland (table 6). These experiments indicate that the gonadotropic principle has no thyrotropic properties.

TABLE 6.—*Results with Gonadotropic Principle from Urine of Pregnant Women*

Dog No.	Initial Weight, Kg.	Method	Duration of Experiment, Days	Clinical Appearance	Comparison of First and Second Sections of Thyroid Gland
70	6.2	1 cc. of gonadotropic principle daily	6	Healthy	No change
72	5.3	1 cc. of gonadotropic principle daily	11	Sick; distemper	No change
73	4.2	1 cc. of gonadotropic principle daily	12	Healthy	No change
74	3.4	1 cc. of gonadotropic principle daily	25	Healthy	No change
71	6.6	1 cc. of gonadotropic principle daily	51	Healthy	No change

EXPERIMENTS ON GUINEA-PIGS TO TEST THE EFFICIENCY OF ANTERIOR PITUITARY EXTRACT AS A STIMULUS FOR THE PRODUCTION OF CHANGES IN THE THYROID GLAND

Eleven guinea-pigs were used to test the efficiency of anterior pituitary extract in the production of changes in the thyroid gland. The disadvantage in using guinea-pigs is that they are too small for preliminary operation and section of the thyroid gland for comparison with later sections. Therefore, the experiments on these animals are not controlled for individual animals. Guinea-pigs are, however, less expensive. Young guinea-pigs about 3 months of age, weighing between 250 and 400 Gm., were chosen. In each instance at the end of the experiment the guinea-pig was killed by injecting 2 cc. of ether into the heart. The thyroid gland was then exposed and measured. In some instances there was a definite isthmus between the two small thin lobes lying close to the trachea. In other instances the isthmus was rudimentary or absent. The parathyroid glands were embedded in the thyroid gland. The thyroid glands were removed and carefully measured, and each gland was sectioned and stained with hematoxylin and eosin.

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[37] The gonadotropic principle used was antuitrin-S. It was supplied by Parke, Davis and Company.

In each instance the pituitary gland, the pars anterior and posterior, was removed and sectioned for microscopic study in order to determine whether a pituitary extract affecting the histologic structure of the thyroid gland might also affect the pituitary gland.

Of the eleven guinea-pigs, three were used as controls. They had been kept in the cages for ten, fourteen and sixty-two days, respectively, while their companions were receiving injections of anterior pituitary extract daily. At the time they were killed they weighed 310, 400 and 650 Gm., respectively. These weights gave some basis for comparison of the size of the thyroid glands of those animals which weighed approximately the same but which had been subjected to intraperitoneal injections of anterior pituitary extract.

Eight of the guinea-pigs were given daily intraperitoneal injections of anterior pituitary extract (1 cc.), an extract of the pars anterior of the pituitary gland. No iodine was used in the experiment, and the guinea-pigs were killed after two, four, six, eight, ten, nineteen, thirty-two and sixty-four days, respectively, by injecting 2 cc. of ether directly into the heart. The thyroid and pituitary glands were recovered and compared microscopically with themselves and with the controls. The extract apparently did not produce any abnormal increase in weight. The sixty-six day control, weighing 650 Gm. (initially 400 Gm.), was compared with guinea-pig 6, weighing 600 Gm. (initially 400 Gm.), after sixty-four daily injections of anterior pituitary extract. Similar comparisons to show this point may be seen in the protocol.

Results of the experiment show that the extract apparently produces some gross change in the thyroid gland. Although the method of measurement was crude, the thyroid gland of the guinea-pig (weight, 600 Gm.) that had received the extract for sixty-four days was slightly greater than that of the control guinea-pig (weight, 650 Gm.) which had been observed for sixty-six days. Similar comparison may be made with other animals in the series with a control of analogous weight. There was no apparent change in the conformity of the gland, and the difference in size detectable by this method is not accepted as unequivocal proof that there is a gross change under these circumstances.

In every instance the pituitary gland showed no recognizable changes microscopically. However, in the thyroid glands from the animals which had received a large number of injections there was unquestionable evidence of hyperplasia (fig. 4). This evidence was seen not only in selected areas but throughout the sections. The microscopic changes indicative of hyperplasia were:

1. The vesicles were smaller and contained less colloid. This reduction in colloid was approximately one third of that in the acini of the controls.

2. In the colloid of the normal guinea-pig, after the thyroid gland was sectioned and stained with hematoxylin and eosin, minute, apparently clear, rounded vesicles were found. These were near the periphery of the colloid. They may be interpreted as evidence of colloid absorption, but this has not been established unequivocally as an accurate interpretation. However, in the guinea-pigs which had received daily doses of anterior pituitary extract over a prolonged period and in which the colloid in the vesicles was diminished, these vesicles were much more numerous and larger and in some instances (guinea-pig 16) were so plentiful that practically all the remaining colloid seemed to be nothing but bubbles.

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38. The anterior pituitary extract used was antuitrin. It was supplied by Parke, Davis and Company.

3. I do not believe that the sign of basophilic staining of the colloid is reliable as a guide to absorption of colloid or hyperactivity of the thyroid gland. It is true that a bluish tinge to the colloid does occur. It was found in the animals that had received anterior pituitary extract over a long period of time, but I also

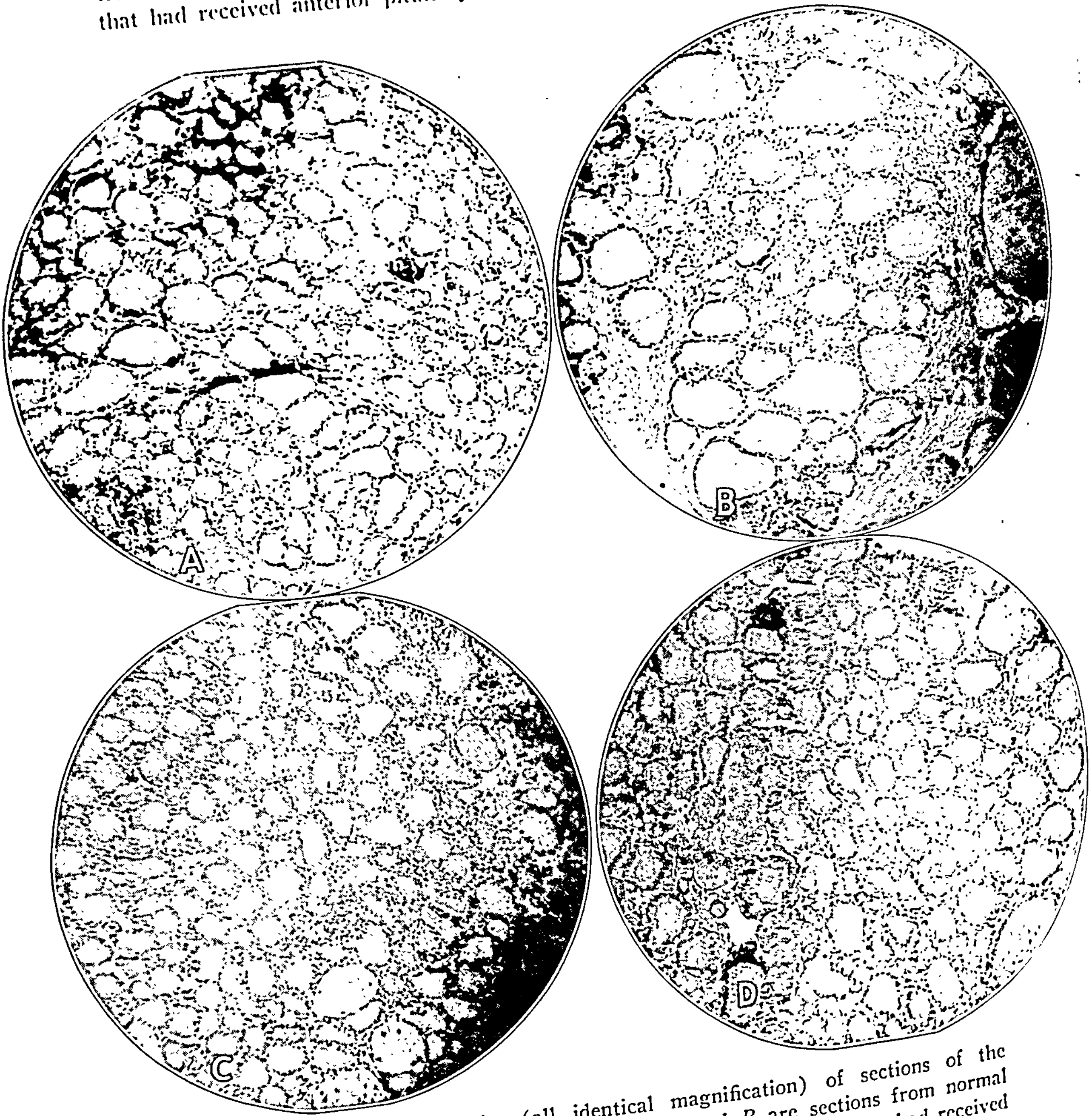

Fig. 4.—Photomicrographs (all identical magnification) of sections of the thyroid gland of four different guinea-pigs. *A* and *B* are sections from normal controls. *C* is a section from the thyroid gland of a guinea-pig which had received daily intraperitoneal injections of anterior pituitary extract for nineteen days. *D* is a section from a guinea-pig which had received injections of anterior pituitary extract daily for ten days. *C* and *D* show smaller acini, more cuboidal cells, less colloid and more vesicles in the colloid than the sections from the controls. The changes in the ten day section are more marked than those in the nineteen day section, but the length of administration does not parallel the degree of change.

found it in some areas in the normal controls. Some normal glands exhibited basophilic colloid more than others, and whereas it seemed to be more constant in animals which had received the extract, its presence is so unreliable in its associations that using it as a sign of activity carries only the weight of presumption.

4. The cells lining the acini of the thyroid gland were definitely more columnar in the animals which had received the extract. The flattest cell in the animals receiving the extract was more columnar than the tallest cells in the acini of the controls. In some acini of the thyroid glands which had been stimulated by the anterior pituitary extract there were high columnar epithelial cells similar to the epithelial cells lining the follicles in the thyroid of a patient with exophthalmic goiter. In no instance were there any infoldings or papillary projections.

TABLE 7.—*Results with Anterior Pituitary Extract*

Guinea-Pig No.	Stimulus	Duration of Experiment, Days	Weights, Gm.		Clinical Appearance of Dog	Thyroid Gland		Microscopic Appearance of Pituitary Body
			Initial	Final		Measurements	Microscopic Appearance	
10	Control	10	200	310	Healthy	R.: 1.0x0.4 cm. L.: 0.9x0.3 cm.	Normal	Normal
1	Control	14	400	400	Healthy	R.: 0.8x0.5 cm. L.: 1.0x0.5 cm.	Normal	Normal
2	Control	66	400	630	Healthy	R.: 1.3x0.6 cm. L.: 1.5x0.5 cm.	Normal	Normal
12	Anterior pituitary extract, 1 cc. daily intraperitoneally	2	220	300	Healthy	R.: 0.7x0.3 cm. L.: 0.6x0.3 cm.	Slight (?) hyperplasia	Normal
13	Anterior pituitary extract, 1 cc. daily intraperitoneally	4	340	380	Healthy	R.: 1.0x0.5 cm. L.: 1.0x0.3 cm.	Questionable hyperplasia	Normal
14	Anterior pituitary extract, 1 cc. daily intraperitoneally	6	260	300	Healthy	R.: 1.0x0.3 cm. L.: 1.0x0.4 cm.	Questionable hyperplasia	Normal
15	Anterior pituitary extract, 1 cc. daily intraperitoneally	8	260	320	Healthy	R.: 1.0x0.3 cm. L.: 1.0x0.4 cm.	Slight hyperactivity	Normal
16	Anterior pituitary extract, 1 cc. daily intraperitoneally	10	260	320	Healthy	R.: 1.2x0.4 cm. L.: 1.5x0.5 cm.	Definite hyperactivity	Normal
4	Anterior pituitary extract, 1 cc. daily intraperitoneally	19	420	335	Healthy	R.: 0.9x0.3 cm. L.: 1.0x0.5 cm.	Hyperactivity	Normal
5	Anterior pituitary extract, 1 cc. daily intraperitoneally	32	330	300	Healthy	R.: 1.0x0.5 cm. L.: 0.9x0.5 cm.	Hyperactivity	Normal
6	Anterior pituitary extract, 1 cc. daily intraperitoneally	64	400	600	Healthy	R.: 1.5x0.5 cm. L.: 1.6x0.5 cm.	Normal	Normal

The most marked evidences of hyperactivity in these sections occurred in the animals receiving the injection for from ten to thirty-two days. It had disappeared in the sixty-four day specimen. Several authors[39] have reported evidence indicating that continued injection of extract of the anterior lobe of the pituitary gland produces changes in the thyroid gland which retrogress toward the normal after different periods of time.

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[39] Loeb and Friedman.[25] Siebert and Thurston.[29] Collip and Anderson.[25]

COMMENT

The conclusions to be drawn from these experiments are merely supportive or nonsupportive of certain still controvertible ideas that extraneous substances stimulate or inactivate the thyroid gland in such a manner as to produce goiter. The experiments support strongly the view that the excess administration of calcium chloride results in changes in the histologic appearance of the thyroid gland. These changes indicate hyperactivity. These experiments do not corroborate the findings of other investigators that infection in the organism and injury to the adrenal gland affects the histologic picture of the thyroid gland.

At the present time these are all merely accumulations of facts which may encourage one to believe that an explanation of the etiology of goiter is nearer. It is still debatable whether the true cause is positive and extraneous, such as calcium or an unknown goitrogenic substance, or positive and autogenous, such as a hormone of the pituitary gland, or negative and autogenous, such as the absence of a hormone, or negative and exogenous, such as a deficiency of some necessary exogenous regulator, for example, iodine. Many conflicting data exist in the literature on the etiology of goiter, but in the main the accumulating weight of evidence is that a hormone of the anterior lobe of the pituitary gland can stimulate the thyroid gland to hyperactivity. It is a much further step to prove that this hormone is the factor outside the thyroid gland which whips it up to hyperactivity in acute hyperthyroidism. It is my experience, as well as that of others, that the thyroid gland removed at operation for hyperthyroidism in patients with acromegaly is a meaty type of thyroid, very parenchymatous and with relatively little colloid in the follicles. In comparing the clinical with the experimental evidence, the interesting question arises whether hyperthyroidism in cases of acromegaly, which is akin to, but clinically not exactly the same as, exophthalmic goiter, results from long-continued excess of this particular thyrotropic hormone of the anterior lobe of the pituitary gland, or whether exophthalmic goiter actually is acute acromegaly or at least a fraction of it. Experimental evidence has far from answered this question.

At the present time there are other possible factors with as much accumulated experimental support, if not in quantity at least in quality. Calcium, an entirely extraneous factor, undoubtedly produces changes in the thyroid gland. Will excess calcium be responsible for one type of goiter and the anterior pituitary extract for another?

Iodine undoubtedly is a factor, but it appears to be an objective and not a subjective one. It is lessened in the goitrous gland, but it seems that something else either fixes it in the blood stream to prevent it from being utilized by the gland or drives it out of the gland by the hyperactivity of the parenchyma. It is true that even when the intake of iodine is undoubtedly adequate under ordinary conditions, the thyroid gland may undergo changes histologically and functionally. Iodine in excess of the normal intake may mitigate the action of the additional factor, but the additional factor is the important one, and that factor as yet has not been found with certainty.

SUMMARY

Experiments on dogs and guinea-pigs gave results which might be safely interpreted to support the following conclusions: Infection in the organism has no specific effect on the histologic picture of the stage of activity of the thyroid gland or on the size of the gland. Injury to or freezing of the adrenal gland in a series of animals resulted in no gross or microscopic changes in the thyroid gland, thus intercepting the inference that elevated basal metabolic rates after similar procedures in the lower animals are the result of hyperthyroidism.

Anterior pituitary-like gonadotropic substances obtained from the urine of pregnant women had no effect on the histologic structure of the thyroid gland when injected daily over varying periods of time. But an extract of the anterior lobe of the pituitary gland produced a histologic picture in the thyroid gland which might be interpreted as increased activity of the gland, viz., disappearance of colloid or diminution of the amount of colloid in the acini; an increase in the size of the epithelial cells, changing their form from low cuboidal to high columnar epithelium, and an increase in the number of vacuoles in the colloid, possibly an indication of its absorbability.

Calcium chloride when added to the drinking water produced definite histologic changes in the thyroid gland of animals which had been on the regimen eighty days or longer. The histologic changes were similar to those described as the result of the administration of anterior pituitary extract; viz., less colloid, larger epithelial cells and more vacuoles in the remaining colloid.

CONGENITAL DISLOCATION OF THE SHOULDER AND OTHER ANOMALIES

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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A case is presented of dislocation of both shoulders since birth. Whether the deformity was truly congenital in the sense of an intra-uterine maldevelopment or whether it was incidental to trauma at birth cannot be stated with certainty. Many dislocations reported as congenital, that is, as intra-uterine, are of paralytic origin or are possibly caused by trauma at birth. The case presented here illustrates the difficulty that arises in determining the etiologic factor of "congenital dislocations of the shoulder." Because of several other rare deformities, namely, amyoplasia congenita, congenital radio-ulnar synostoses, ectrodactylia and cervical ribs, this case assumes added interest.

Some authors (Kirmisson and Broca) have been unable to produce dislocation of the shoulder joint experimentally in a new-born child and hence have concluded that a dislocation cannot result from the trauma of birth. There is no doubt, however, that paralysis caused by injury to the brachial plexus will cause or accompany dislocation of the shoulder. Dislocations due to paralysis or to trauma at birth may be differentiated from truly congenital dislocations (1) by the history of an abnormal, a difficult or an unusual instrumental delivery; (2) by the presence of paralyzed or paretic muscle groups in the involved extremity or (3) by the absence of other definitely congenital anomalies which favor the congenital nature of the deformity. Because the differentiation of the two types of dislocations is by exclusion, it is frequently difficult and at times impossible to classify a given case properly.

Greig[1] in 1923 thoroughly reviewed the literature on congenital dislocations of the shoulder, judging the truly congenital nature of the dislocations by the birth history, the presence or absence of paretic musculature and the condition of the child immediately after birth. He found twelve reported cases in which there was no doubt in his mind that the deformity was a primary intra-uterine developmental defect. Many dislocations of secondary types, comprising the disloca-

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[1] Greig, D. M.: True Congenital Dislocation of Shoulder, Edinburgh M. J. **30**:157-175 (April) 1923.

tions associated with the trauma of birth, are seen in orthopedic clinics and practices.

A critical survey of the cases reviewed by Greig leads me to include only ten instead of twelve cases as instances of truly congenital dislocation. In the cases recorded by Abadie and Pelissier,[1a] Cumston,[2] Hebert,[3] Hitzrot,[4] Kelley,[5] Léniez,[6] Openshaw,[7] Peckham[8] and Scudder[9] (two cases) the condition can be neither of traumatic nor of paralytic origin. Küster's[10] patient had a spastic upper extremity. The history of the birth is not mentioned in his report, and the condition seems to be spastic paralysis with associated dislocation of the humerus. Hartwell's[11] description discloses paralysis of the deltoid muscle, so that his case cannot be placed in the group of instances of primary dislocation.

Since the publication of Greig's series in 1923, eight additional cases of this deformity have been reported; seven are instances of the truly congenital type, and the origin of the dislocation in the other is doubtful.

Frosch[12] in 1925 presented three cases, in each of which the dislocation was bilateral. He expressed the belief that the abscence of trauma at birth and of muscular paralysis eliminated the possibility that the dislocation was anything but a developmental anomaly. Roentgenograms of the three patients showed an abnormally flattened glenoid fossa. This anomaly was also bilateral in all three patients.

[1a] Abadie, J., and Pelissier, G.: Luxation congénitale de l'épaule, Rev. d'orthop. **1**:245-260 (March) 1910.

[2] Cumston, C. G.: Congenital Dislocation of the Shoulder, Am. J. M. Sc. **125**:967-984 (June) 1903.

[3] Hebert, P.: Absence congénitale des voies biliaires extra-hépatiques chez un enfant d'un mois présentant en outre un persistance du trou de Botal, et une malformation congénitale du membre supérieur gauche, avec luxation de l'épaule, absence du radius et main bote cubitale, Rev. d'orthop. **5**:57-66 (Jan.) 1904.

[4] Hitzrot, J. M.: Posterior Congenital Dislocation of the Left Shoulder, Ann. Surg. **55**:622-623 (April) 1912.

[5] Kelley, S. W.: Surgical Diseases of Children, ed. 3, St. Louis, C. V. Mosby Company, 1929.

[6] Léniez: Un cas de luxation congénitale de l'épaule, Rev. d'orthop. **10**:159-164 (March) 1909.

[7] Openshaw, T. H.: Case of Multiple Dislocation, Including Congenital Dislocation of Both Hips, in a Child Aged Two Weeks, Incontestably the Result of Malposition in Utero, Proc. Roy. Soc. Med. (Clin. Sect.) **1**:106, 1907-1908.

[8] Peckham, F. E.: Two Cases of Congenital Dislocation of the Shoulder Joint, Arch. Pediat. **21**:509-511 (July) 1904.

[9] Scudder, C. L.: Congenital Dislocation of the Shoulder-Joint: Report of Two Cases, Arch. Pediat. **7**:260-269 (April) 1890.

[10] Küster, E.: Ein 1 jähriges Kind mit angeborenen doppelseitiger Luxation des Oberarmkopfes nach hinten, Berl. klin. Wchnschr. **16**:9 (Jan. 6) 1879.

[11] Hartwell: Deformity of the Shoulder Joint, Ann. Surg. **45**:454 (March) 1907.

[12] Frosch, L.: Congenital Subluxation of Shoulders, Klin. Wchnschr. **4**:701-702 (April 9) 1925.

A case of bilateral dislocation of the humerus was reported in 1928 by Edwards.[13] Autopsy on this man, who was 46 years of age, revealed the glenoid fossa to be absent, its place being taken by the neck of the scapula. The biceps tendon (long head) arose from a point corresponding to the supraglenoid tubercle. Although his delivery was said to have been difficult, there was no accompanying paralysis. Here is another case similar to the one I am reporting, in which the dislocation cannot be classified with surety as a congenital anomaly. The difficult birth casts a shadow of doubt on its intra-uterine causation despite the developmentally retarded shoulder joint disclosed at autopsy.

The next case to be found in the literature is that of Wolff,[14] who in 1929 described a patient in whose family a similar deformity had been known for the previous three generations. Other anomalies, such as absence of a thumb and amniotic bands, were present. There was, in addition, rigidity of the elbows and interphalangeal joints, apparently congenital, with absence of motion in the radio-ulnar articulations. This description practically duplicates that of my patient. The author does not comment on the presence of the congenital articular rigidity, although his case is apparently the first ever reported in which both anomalies were present—congenital dislocation of the shoulder and congenital articular rigidity (arthrogryposis, multiple congenital contractures and amyoplasia congenita). If the dislocation in the case presented here is truly congenital, then the case will be the second in the literature in which both deformities are reported.

To Valentin[15] is credited the report of three cases in one family, which he described in 1931. The two brothers and one sister had varying degrees of functional inpairment of their arms, but in none was the malfunction severe. In all three roentgenograms revealed posterior dislocation of the head of the humerus and flattening of the glenoid fossa. Birth was normal in each of the siblings.

Can the following case be added to this small group of true congenital dislocations?

REPORT OF CASE

L. C., a boy, was brought to the orthopedic clinic at the State University of Iowa at the age of 4 years because of the abnormal appearance and weakness of both his upper extremities. He has three brothers, all older than he and none with any known abnormalities. An infant who would have been his uncle was stillborn, with "deformed feet and ankles." No other deformity was revealed in the familial history.

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[13] Edwards, H.: Congenital Displacement of Shoulder Joint, *J. Anat.* **62:** 177-182 (Jan.) 1928.

[14] Wolff, G.: Ueber einen Fall von kongenitaler Schulterluxation, Ztschr. f. orthop. Chir. **51:**199-209 (Jan. 11) 1929.

[15] Valentin, B.: Die kongenitale Schulterluxation, Bericht über drei Fälle in einer Familie, Ztschr. f. orthop. Chir. **55:**229-240, 1931.

The patient's mother stated that his delivery was "long and hard" and that he weighed 13½ pounds (6,125 Gm.). A forceps was not used. His neck was encircled twice by the umbilical cord; he did not cry for twenty minutes after birth. His arms and hands "did not look right" immediately after birth, his mother affirmed. When he was 2 months of age a rudimentary right thumb was removed by the family physician.

When the patient first entered the clinic, eight years before the present examination, several abnormalities were noted. The clavicles were extremely prominent, and their normal curvature was increased. Both shoulders had a squared instead of the usual rounded appearance. This squaring of the shoulders was caused by the accentuated acromion processes with the displacement of the heads of the humeri inferiorly, out of the glenoid cavities. On the left shoulder there was a gap of about 2 inches (5 cm.) between the head of the humerus and the acromion process.

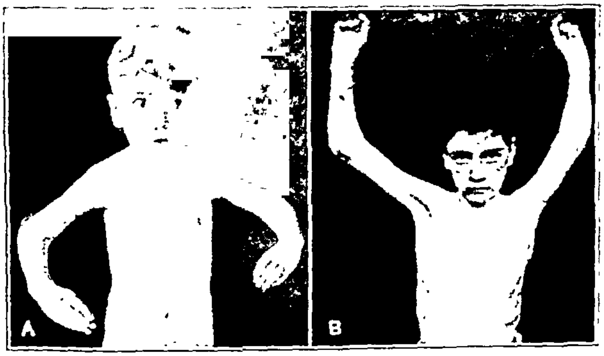

Fig. 1.—*A*, the boy as he appeared on his first visit to the clinic. The humeri were not abducted to their maximum, but merely enough to depict the hands clearly. *B*, photograph taken on March 1, 1933, after capsulotomy on both shoulder joints, augmented by a Nicola suspension operation on the head of the right humerus.

Motion in the shoulder joints in degrees was as follows:

	Right	Left
Flexion	0- 95	0- 90
Extension	0- 15	0- 10
Abduction	0-120	0-100
Adduction	0- 25	0- 25
External rotation	0- 30	0- 20
Internal rotation	0- 10	0- 20

There were slight atrophy and weakness of the shoulder muscles on both sides, that is, the deltoid, pectoralis major, latissimus dorsi, supraspinatus, infraspinatus, biceps and triceps muscles.

A flexion contracture of 30 degrees was found in the left elbow, and of 10 degrees in the right, so that the angle of maximum extension on the right elbow was 170 degrees, and of maximum flexion, 30 degrees. On the left side the values were, respectively, 150 and 40 degrees. Pronation and supination movements in the forearms were absent; the left forearm was fixed in a position of 50 degrees of pronation, and the right was held in a neutral or pistol grip position.

There was no limitation of motion in the wrist joints proper. There was dorsiflexion of from 180 to 135 degrees and palmar flexion of from 180 to 110 degrees. The range of motion in the two wrists was practically identical.

The entire first ray of the right hand was absent; no metacarpal or phalanges of the thumb were present. On the left hand there were a diminutive first metacarpal and two phalanges attached to the index finger at the base of its first phalanx. The boy could not control this digit voluntarily.

Motion in the fingers was limited as follows:

	Right	Left	Normal
Metacarpophalangeal joints	180-140	180-150	180-90
First interphalangeal joint............	180- 95	180-130	180-80
Second interphalangeal joint..........	180-165	175-180	180-90

There was slightly less motion in the digits on the radial side of the hand than in those on the ulnar side.

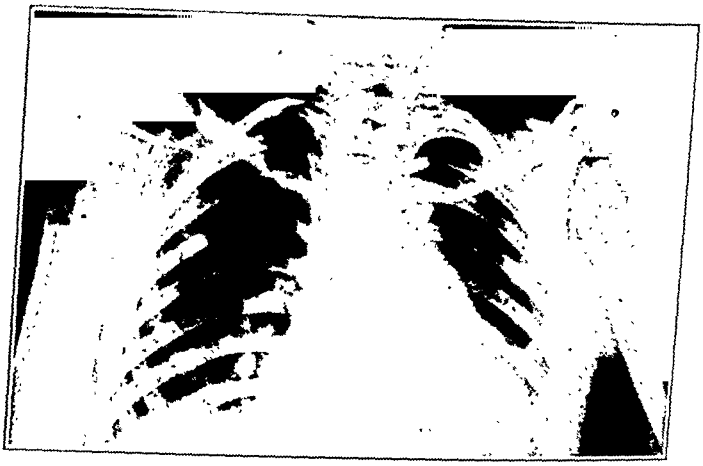

Fig. 2.—Roentgenogram taken on Aug. 8, 1932, four years after capsulotomy on both shoulder joints and one month after the Nicola type of operation of the right shoulder. The pyramidal-shaped heads of the humeri and the shallow glenoid fossae are evident. The rudimentary seventh cervical ribs can be seen.

Both lower extremities were normal; there was no limitation of motion in any of their joints. Only one additional anomaly was found on clinical examination—a patent ductus arteriosus which was causing no symptoms.

Roentgenograms showed maldevelopment of the glenoid fossae with small scapulae, but with large coracoid processes. The heads of the humeri were found to be hypoplastic, especially on the right, where the head was more pyramidal than spherical and was quite a distance below and lateral to the glenoid fossa. Rudimentary seventh cervical ribs were present bilaterally. The upper end of the right ulna appeared deficient anteriorly where the coronoid process formed only a small and flat bony prominence; the semilunar cavity was shallow. The upper radio-ulnar joint appeared to be fused by a bony bridge. Roentgenograms of the left upper extremity were practically identical with those of the right. No other changes were present in the joints of the elbows, wrists and hands.

Operative reefing of the capsules was performed on the right and left shoulder joints. The right shoulder was operated on four weeks after the boy was admitted to the clinic, and the left, eight weeks after his entry. Dislocation recurred spontaneously on the right side three years after operation. A typical Nicola suspension operation was performed on the right shoulder in July 1932, four years after the reefing operation. At the time of the second operation it was found that relaxation of the capsule had recurred. The right joint has remained in place since the second operation, but the boy complained of an occasional slipping sensation until one year prior to the present examination (June 2, 1936). Since then he has noted no feeling of instability in the joint and is well pleased with the results of the operations. The left shoulder has remained in the glenoid fossa ever since the capsular reefing was performed in 1929. Despite the mild limitation of motion in the shoulder joints, the boy now has excellent function of both shoulders.

The rudimentary left thumb was removed in 1928, since it was useless and interfered with flexion of the other fingers.

When the patient was examined on June 2, 1936, the only changes that could be noted from his examination eight years previously were the results of the surgical procedures and the increase in size of his entire body. The heads of the humeri were found in close proximity to the glenoid fossae, both on direct and on roentgenographic examination. The relaxation and dislocation had been replaced by stability of the joints in their entire range of motion. Other joints were practically unchanged (they had the same degree of mobility), but there had been an increase in muscular strength of the shoulder girdle, so that now muscle strength was within normal limits. The patient performs many varieties of manual tasks but has slight awkwardness in grasping tools.

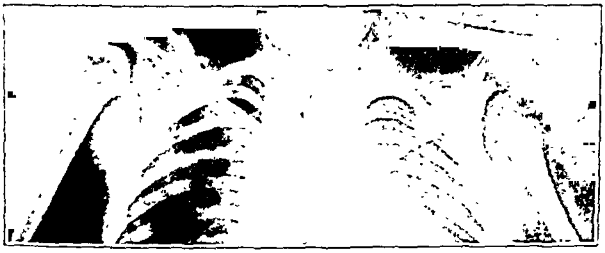

Fig. 3.—Roentgenograms taken on June 2, 1936. The heads of the humeri are rounder, and the humeri and the glenoid fossae are less abnormal than when the first roentgenograms were taken.

The diagnosis, then, is dislocation of the shoulders, with multiple congenital anomalies, namely, contracture of the joints, synostosis of the radius and ulna, ectrodactylism, cervical ribs and a patent ductus arteriosus.

What was the cause of the dislocated shoulders in this patient? He weighed 13½ pounds at birth, and labor was abnormally difficult. Paralysis of the brachial plexus may be discarded as the cause of the dislocation, since no paralyzed muscle could be found. Trauma at birth cannot be so easily disregarded. The prolonged and arduous labor, plus the large weight at birth, point to trauma as the etiologic factor. It has been noted that experimentally it is impossible to produce a traumatic dislocation in a new-born child. The presence of numerous congenital deformities and the deformed glenoid fossae greatly increase the probability of the congenital nature of the deformity. No certain classification of the anomaly as being congenital can be made.

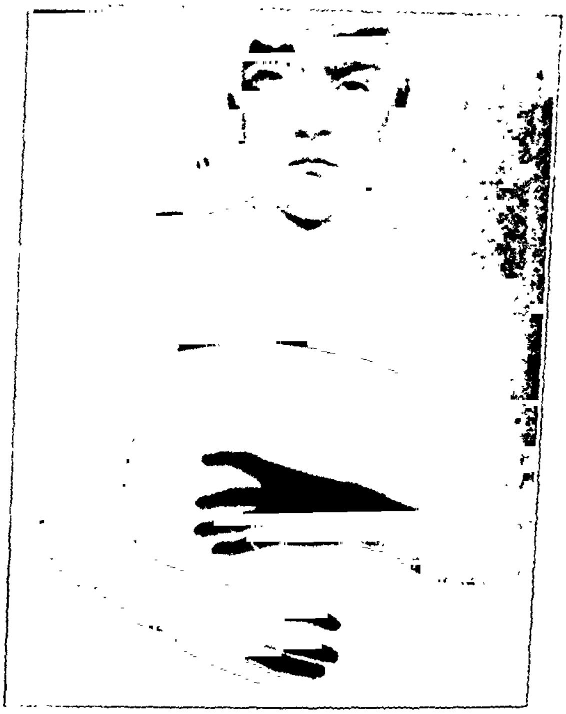

Fig. 4.—The patient as he appeared in May 1936.

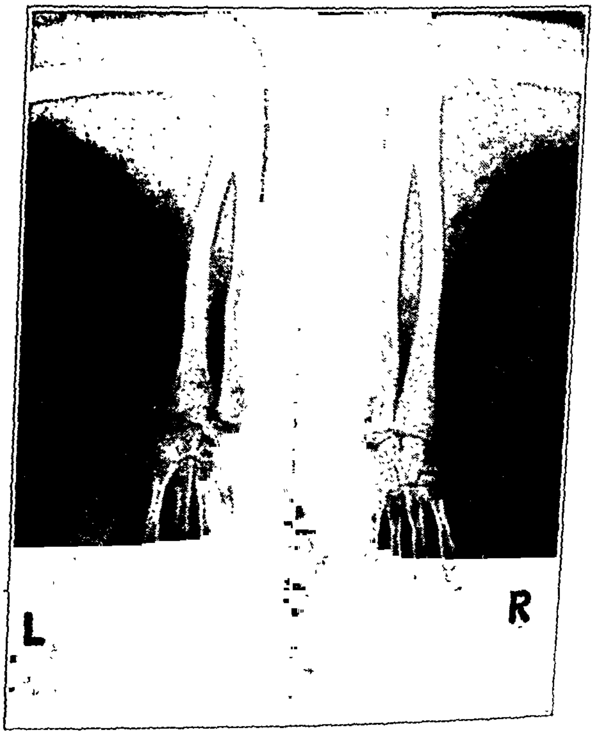

Fig. 5.—Roentgenogram taken in May 1936, showing only four skeletal rays on each hand.

TREATMENT

The treatment of congenital dislocation of the shoulder falls into three types: (1) no therapy, (2) manipulative treatment and (3) operative treatment. Léniez[6] and Ranzi,[16] among others, offered their patients no treatment.

Whitman[17] advised manipulation of the shoulders similar to the manipulation of a congenitally dislocated hip; he concluded that a plaster bandage should be used to immobilize the reduced shoulder.

Cumston[2] reported excellent function following a simple open reduction, whereas Roberts,[18] Peckham[19] and Hitzrot,[4] obtained good functional results for at least five years after resection of the head of the humerus. Scudder[20] suggested three methods of attack: (1) wiring the head of the humerus to the glenoid cavity, almost effecting an arthrodesis of the joints: (2) excision of the head of the humerus, and (3) resection of the portion of the spine of the scapula obstructing motion.

The patient in the case reported here had three separate operations. The joint capsule was reefed on the right and the left shoulders in an attempt to overcome the dislocation by shortening the pendulous capsule. The humeri remained in place for the following three years. After Nicola's report in 1929 on the treatment of recurrent dislocation of the shoulder, the method he described was used on the right shoulder. These operations yielded satisfactory results in this case.

Congenital contracture of the joint was brought to the attention of the medical profession by Stern,[21] who in 1923 named the syndrome arthrogryposis multiplex congenita. He observed four cases. In one infant a congenital dislocation of the hip was also noted; in another there was subluxation of the tibia on the femur, but in no case was a dislocation of the shoulder present. There was extension contracture of the joints in his cases, which he believed to be caused by an incomplete fibrous ankylosis of the joints. He considered this fibrous degeneration to be verified by the capsular thickening shown in the roentgenograms.

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[16] Ranzi, E.: Ein Fall von doppelseitige (congenitaler) Schulterluxation nach rückwärts, Zentralbl. f. Chir. **39**:1144 (Oct.) 1904.

[17] Whitman, R.: The Treatment of Congenital and Acquired Luxations at the Shoulder in Childhood, Ann. Surg. **42**:110-115 (July) 1905.

[18] Roberts, J. B.: A Case of Excision of the Head of the Humerus for Congenital Subacromial Dislocation of the Humerus. Am. J. M. Sc. **130**:1001-1007 (Dec.) 1905; The Result Five Years After Excision of the Humeral Head for Congenital Subacronial Dislocation of the Humerus, Ann. Surg. **49**:431-432 (March) 1909.

[19] Peckham, F. E.: A Case of Congenital Dislocation of the Shoulder Joint, Boston M. & S. J. **176**:355-356 (July) 1917.

[20] Scudder, C. L.: Congenital Dislocation of the Shoulder-Joint, Am. J. M. Sc. **115**:125-131 (Feb.) 1898.

[21] Stern, W. G.: Arthrogryposis Multiplex Congenita, J. A. M. A. **81**:1507-1510 (Nov. 3) 1923.

Stern, however, was not the first to describe this congenital anomaly. Wunsch [22] in 1901 presented a case under the term "multiple congenital contractures" and reviewed seven cases which had been reported prior to 1900. His reports include the cases of Zengerly. Schanz, J. Wolf, Bedner, Baumgartner, Redard and Wirt.

Since the eight cases reported by Wunsch in 1901, there have been at least twenty-one others recorded: four by Rocher [23] in 1918, five by Magnus in 1903,[24] 1928 and 1930, four by Sheldon [25] in 1932, three by Scarlini [26] in 1926, two by Lewin [27] in 1925, one each by Comby [28] and Price [29] in 1933 and one by Marconi [30] in 1922. At the orthopedic clinic in Iowa City nineteen cases of multiple congenital contractures have been seen since 1915.

The exact nature of this syndrome is still unknown. Price found changes in the spinal cord consisting of meningeal inflammation plus a lack of myelin in the anterior and posterior roots in a patient who came to autopsy. The muscle tissue showed partial degeneration, fibrous and fatty.

He expressed the belief that the degeneration of the cord and muscle proves that the condition cannot be a primary change in the joint, as Stern and previous authors emphasized.

Sheldon proposed the term "amyoplasia congenita" instead of the previous names used—multiple articular rigidity and arthrogryposis multiplex congenita. The name amyoplasia congenita does not describe the most important feature of the anomaly—deficient motion of the joints. Since only one autopsy report (Price) is available at this date, the underlying pathologic changes are still a matter of conjecture.

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[22] Wunsch, Max: Multiple congenitale Contracturen, Arch. f. Kinderh. **121**:161-178, 1901.

[23] Rocher, H. L.: A propos d'un cas de luxation congénitale postérieure de l'épaule droite, Arch. de méd. d. enf. **21**:359-364 (July) 1918.

[24] Magnus, F.: Ein Fall von multiplen congenitalen Contracturen mit Muskeldefecten, Ztschr. f. orthop. Chir. **11**:424-431, 1903.

[25] Sheldon, W.: Amyoplasia Congenita (Multiple Congenital Articular Rigidity: Arthrogryposis Multiplex Congenita), Arch. Dis. Childhood **7**:117-136 (June) 1932.

[26] Scarlini, G.: Sulle rigidita articolare congenita multiple e sul loro trattamento, Arch. di ortop. **42**:453-494, 1926.

[27] Lewin, P.: Arthrogryposis Multiplex Congenita, J. Bone & Joint Surg. **7**:630-636 (July) 1925.

[28] Comby, J.: L'amyoplasie congénitale ou rigidite articulaire multiple congénitale, Arch. de méd. d. enf. **36**:171-177 (March) 1933.

[29] Price, D. S.: Case of Amyoplasia Congenita with Pathological Report, Arch. Dis. Childhood **8**:343-354 (Oct.) 1933.

[30] Marconi, S.: Rigidita articolari congenite multiple, Arch. di orthop. **38**:248-262, 1922.

There are no specific joints that are contracted in this congenital condition. All four limbs may be affected, as in Sheldon's case, or only the arms, as in Rocher's case and in the case reported here. The contracture may be either an extension (Stern) or a flexion (Scarlini) contracture.

In the case presented here there was limitation of motion in both elbows and wrists and in all the fingers. The absence of pronation and supination cannot be included in this syndrome since a bilateral radio-ulnar synostosis prevented this movement.

Althoug the contractures of the joints were not extreme, they were definite enough to preclude the possibility of the rigidity being within normal limits. As the rigidity of the joints had been present since birth, the diagnosis was limited to a congenital anomaly as the cause of the deformity.

Treatment for congenital articular rigidity varies. Scarlini successfully employed combined osteotomy and traction to correct the flexion deformity of the knee. He could not procure any increase of motion in the affected joints. Manipulation under anesthesia is of no value in decreasing the motion in the joints (Comby). Active and passive motion under skilled guidance in addition to reconstructive surgical measures seem to give the best results (Stern).

The radio-ulnar synostosis noted in this patient is not a very rare anomaly. Fahlstrom[31] collected one hundred and eighty-five reported cases in 1932. In some patients surgical intervention has been attempted with but little success (Blaine[32]). In most instances, as in this case, function is so little impaired as to discourage operative intervention.

The absence of thumbs or fingers is termed ectrodactylia or oligodactylia. The name ectrodactylia is also applied to fingers which are not entirely absent but are represented by small osseous nodules corresponding to the phalanges (Steindler[33]). Removal of these functionless appendages was performed in this case, although Kanavel[34] has not found operation necessary in his patients.

The bilateral seventh cervical ribs have given rise to no symptoms and therefore have not been treated.

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[31] Fahlstrom, S.: Radio-Ulnar Synostosis: Historical Review and Case Report, J. Bone & Joint Surg. **14**:395-403 (April) 1932.

[32] Blaine, E. S.: Congenital Radio-Ulnar Synostosis, with Report of a Case, Am. J. Surg. **8**:429-434 (Feb.) 1930.

[33] Steindler, A.: Reconstructive Surgery of the Upper Extremity, New York. D. Appleton and Company, 1923, pp. 228-229.

[34] Kanavel, A. B.: Congenital Malformations of the Hands, Arch. Surg. **25**: 1-53 (July); 282-320 (Aug.) 1932.

SUMMARY

A case is reported of a patient who presented several skeletal deformities, bilateral dislocation of the shoulders, congenital articular rigidity, congenital radio-ulnar synostoses, ectrodactylism and cervical ribs. Dislocation of both shoulders had been present since birth, but whether the dislocation was truly congenital is not certain. This case exemplifies the difficulty in ascertaining the causative factors in reported cases of congenital dislocations of the shoulders.

A review of the literature on some of the anomalous conditions is included.

HYPERPLASIA AND NEOPLASIA OF THE INTERSTITIAL CELLS OF THE TESTICLE

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Considerable confusion exists as to the type and terminology of testicular tumors. Many varieties of tumor arise from the complex elements composing the testicle, and identities are further obscured by the possibility of teratoid origin. No attempt will be made to classify tumors of the testicle, but it may be stated that the scope of pure simple tumors of the testicle has been greatly narrowed by the study of teratoma testis and its derivatives. Ewing stated that all the common and nearly all the rarer testicular tumors arise from totipotent sex cells and that the monodermal forms represent one-sided developments of tridermal teratomas. Only rarely, he stated, do the stroma, duct cells, interstitial cells and adult seminiferous tubules give rise to characteristic growths. His view is more extreme than that of most, who separate from the group of teratoma testis and its derivatives the seminoma, or spermatocytoma, as being derived from adult seminal epithelium rather than from totipotent sex cells and also various rare tumor types supposedly derived from the supporting structures, which Ewing in large part includes in the teratoid group. From the major number of classifications, interstitial cell tumor, apparently because of its rarity, is omitted or given only passing mention.

Only isolated case reports of interstitial cell tumor are to be found in the literature. Even among these few, however, are found a number which are obviously spurious and others in which the description is too brief or the structural picture not sufficiently clear for a definite diagnosis to be established. Moreover, marked hyperplastic states of the interstitial cells have also been misinterpreted as actual new growths arising from these cells.

Though the primary concern of this paper is with tumors of the interstitial cells of the testicle, the rather more common hyperplasia of these cells will be dealt with first in order to avoid confusion between the two and to clarify the criteria on which a diagnosis of interstitial cell tumor may be based. The reported cases of interstitial cell tumor in human beings will then be critically reviewed. For completeness, hyperplasia and neoplasia of the interstitial cells as occurring in animals

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From the Surgical Service of Dr. Harold Neuhof and the Department of Laboratories, Mount Sinai Hospital.

will be dealt with briefly. Finally, a report of a case of *interstitial cell tumor* occurring in the surgical service of Dr. Harold Neuhof, at the Mount Sinai Hospital, will be presented.

NORMAL HISTOLOGIC STRUCTURE AND OCCURRENCE OF THE INTERSTITIAL CELLS

The interstitial cells of the testicle (cells of Leydig) are modified connective tissue cells of epithelial contour lying in the testicular stroma between the seminiferous tubules. They vary considerably in number in different persons and in different periods of development. The cells are large and irregularly spherical or polyhedral; transition forms are common. The nuclei are relatively small and usually spherical and for the most part are situated eccentrically within the cells. They are pale and contain a sparse amount of chromatin and one or two nucleoli. Occasionally a cell has two nuclei. The characteristic feature of the cell is various inclusions in the abundant cytoplasm. In the fresh state the protoplasm is filled with highly refractile granules, a large part of which represent neutral fat or lipoids (cephalin, sometimes cholesterol esters). Numerous brownish granules of varying size having properties of waste pigment (lipofuchsin) are present. Other inclusions are droplets of colloid-like substance, granules of an indefinable nature and peculiar heavily staining rod-shaped crystalloids with rounded or pointed ends, known as Reincke's crystalloids (Maximow, Cowdry, Piersol and Kaufmann).

In the fetus interstitial cells are quite numerous. After birth they are reduced in number, being replaced by increased connective tissue. By the age of 8 very few are to be found. Until puberty the cells are not absolutely identical with those of the adult. From the time of puberty the cells increase in number and assume their characteristic appearance. Pigment does not appear until adulthood. At this time the cells are quite characteristic, are easier to differentiate and are collected in groups usually of four or five, though sometimes of as many as fifty. During adult life the cells decrease in number, so they frequently are hard to find and rarely even entirely disappear. Usually, however, though reduced, they are more numerous than prior to puberty. Finally, with old age, in the normal senile testis an inconstant increase in interstitial cells accompanies an increase in interstitial tissue, which occurs at the expense of the seminiferous tubules (Spangaro, Finotti and Kaufmann).

HYPERPLASIA OF INTERSTITIAL CELLS

Apart from normal variations in the number of interstitial cells, hyperplasia of varying degree is found in numerous disease and experimental states. At times the hyperplasia is so marked that the impression of beginning new growth is obtained. However, that this increase in interstitial cells is secondary to the tubular atrophy which is invariably present will readily be seen from the nature of the material in which hyperplasia is observed.

Atrophic Senile Testes.—Spangaro described atrophic senile testes in contradistinction to normal senile testes. In the former the parenchymal atrophy is considerably more marked. He arbitrarily marked off three stages of atrophy on the basis of the degree of tubular degeneration, which progresses from cessation of spermatogenesis, to a decrease in the seminal cells, to a diminution in the caliber of the tubules with a thickening of their walls. Hyalinized connective tissue is laid down internal to the elastic layer of the tubular wall and increases progressively at the expense of this layer. The hyperplasia of the interstitial cells is marked and is present in a degree proportional to the stage of atrophy. The cells are grouped closely together in nests between and sometimes surrounding atrophic tubules. In three of fifty-two cases studied by Spangaro they formed nodes of from 0.5 to 1.8 mm. in diameter, which could be seen without the aid of a microscope. The cells are richer in pigment than the cells in the normal senile testes. Their death is marked by the appearance of vacuoles in the cell body. Of significance was the finding by Spangaro of apparent invasion of the atrophic tubules by the proliferating interstitial cells, which were observed in the walls of the tubules and occasionally even in their lumens. By elastic tissue stains he demonstrated that this invasion occurred only in cases of extreme atrophy when the elastic layer of the tubular wall was almost completely destroyed. What occurred, according to Spangaro, was not a true invasion but rather a consequence of the tremendous increase of interstitial cells which the altered tubules were not able to resist, the cells virtually growing into a wall that was already destroyed.

Chronic Illness.—In chronic illnesses in which cachexia is prominent, testicular atrophy and hyperplasia of the interstitial cells are features. According to Langhans, atrophy of the testicular tubules is quite common in tuberculosis and syphilis and less frequent in tumors of the testis. The characteristic change he described was a thickening of the connective tissue wall of the tubules, the thickened membrana propria showing an outer fibrous and an inner glistening homogeneous layer. The thickening at times led to obliteration of the tubular lumen. The interstitial stroma was broadened, and the blood vessels were injected. In some cases the interstitial cells were quite rich, sometimes near the rete and sometimes throughout the entire testis. In tumors of the testis hyperplasia of the interstitial cells was found in the portions of the testicle not involved by the new growth.

Hansemann also found this increase in interstitial cells in chronic cachectic conditions (tuberculosis, carcinoma, syphilis and pernicious anemia) occurring even without involvement of the testis by the disease. Pigment was not always present in the cells. In a 44 year old man with pernicious anemia there was a marked increase in the Leydig cells. The testes were large, firm and gray-brown. The tubules could not be drawn out and were separated by broad strands of large pigmented interstitial cells. Similar changes were cited in a 50 year old man with chronic alcoholism and hemochromatosis of the intestines and the mesenteric lymph nodes.

Lubarsch reported an increase in interstitial cells in chronic phthisis and in the cachexia of carcinoma. He made the point that when the tuberculous process involves the testicle, the increase in the interstitial cells is not present in the tuberculous foci but in the remaining uninvolved portion of the testis.

Cordes studied the testes of thirty-one patients dying of chronic illnesses. There were fourteen who died of tuberculosis, mainly pulmonary, between the ages of 18 and 78. In seven there was a definite increase in the interstitial cells, with an absence of spermatogenesis, and in five of these pigment was present in the interstitial cells. Seven of the patients, from 30 to 63 years of age, died of a malignant growth, and in two there was an increase in the interstitial cells, with pigment present in the cytoplasm in one. Spermatogenesis was entirely absent in the testes of one of these patients and only occasionally seen in the testes of the other. In a 53 year old man dying of aneurysm of the aorta there was an increase of richly pigmented interstitial cells; also in a 68 year old man who died of chronic endocarditis. The testicles of seven of the nine remaining patients, consisting of four with chronic nephritis and five with a chronic cardiac condition or diabetes and varying in age from 28 to 92 years, showed active spermatogenesis. In none of these was an increase in interstitial cells noted.

Bouin and Ancel also noted an increase in the "interstitial gland" in chronic diseases (chronic pneumonia, generalized arteriosclerosis, renal sclerosis with cachexia, carcinoma and, particularly, phthisis). Regressive changes in the seminiferous tubules accompanied by progressive fibrotic processes in the interstitial tissue were noted by Simmonds to occur in chronic circulatory disease, arteriosclerosis, leprosy and syphilis. In any of these types of fibrosis he observed that there might be an increase in the interstitial cells.

Koch studied the testicles removed from three patients who died of generalized tuberculosis. In all he found a great increase in interstitial cells. In contrast, in local tuberculosis the interstitial cells were in the background. In the testicles of a 64 year old man with an inoperable carcinoma of the stomach and of a 56 year old man with generalized arteriosclerosis, myocarditis and emphysema, he found an absence of well preserved tubules and the presence of dense masses of pigmented interstitial cells arranged in "liver-like formation." He found similar changes in the testicles of two patients with hepatic cirrhosis. In cases of diabetes mellitus in which there was some degree of cachexia these changes were present to a less marked degree. The testicles of six syphilitic persons were studied. In three an increase in interstitial cells was observed. These three patients, however, presented an additional systemic disease, hepatic cirrhosis, phthisis and a malignant growth, respectively. Koch concluded that the cachexia, with its accompanying tubular degeneration, was the essential and primary feature. Proliferation of the interstitial cells was secondary to the decreased pressure of the tissue resulting from parenchymal atrophy and would occur in all conditions in which there were severe changes in the tubules. Further tubular atrophy might then be caused by the pressure of the augmented interstitial tissue.

Hyperplasia of the interstitial cells in chronic cachectic states was discussed by Stoppato, with similar conclusions. Berblinger reported marked tubular atrophy and extreme proliferation of interstitial cells in a 26 year old underdeveloped man with tuberculosis of the lungs and lymph nodes and miliary tuberculosis. In a 61 year old man suffering from generalized severe arteriosclerosis and gout, a focal proliferation of interstitial cells was present around the remnants of the tubuli contorti. Finally, Kaufmann stated that in general diseases in which spermatogenesis decreases an increase in interstitial cells occurs.

Chronic Alcoholism.—Chronic alcoholism similarly leads to progressive alteration in the tubules of the testes, which frequently is accompanied by proliferation of the interstitial cells. Weichselbaum, and Weichselbaum and Kyrle reported fifty-seven cases of chronic alcoholism. The testes were all smaller than normal. Three stages of tubular atrophy were found: (1) cessation of spermatogenesis, (2) a decrease in the seminal cells and (3) diminution in the size of the seminiferous tubules, with thickening of the tubular wall and occasionally complete obliteration of the tubules. A widespread focal increase in interstitial cells was observed in all cases. They concluded that chronic alcoholism leads to changes in the tubules regardless of those present due to senility or to disease. However, their conclusions are not completely warranted, as thirty-three of the patients died of hepatic cirrhosis, two died of a combination of delirium tremens and hepatic cirrhosis and eight, though showing signs of chronic alcoholism (edema of the pia-arachnoid, fatty liver, etc.), died of carcinoma, apoplexy, encephalomalacia, chronic tuberculosis, pneumonia and leptomeningitis. Fourteen died of delirium tremens. It is apparent that except in the fourteen cases in which death was directly attributable to delirium tremens, the accompanying condition (hepatic cirrhosis, carcinoma, tuberculosis, etc.) might in itself have been responsible for the hyperplasia of the interstitial cells. Another feature of interest noted was that the changes were greater in degree when cirrhosis of the liver complicated the chronic alcoholism than when other chronic diseases were present concomitantly.

Hansemann, Berblinger and Kaufmann also noted tubular atrophy and hyperplasia of the interstitial cells in the testes of persons with chronic alcoholism.

Acute Illnesses.—In the realm of acute illnesses, Cordes reported the changes in the testes of thirty-six patients. Twenty between the ages of 24 and 59 died of pneumonia. In thirteen of these there was an increase in interstitial cells. Spermatogenesis was absent in seven and sparse in three of the thirteen. Five patients between 26 and 58 died of typhoid. All showed an increase in the interstitial cells. Spermatogenesis was absent in three and only rarely seen in one. The testes of a 19 year old youth dying of tetanus also showed an increase of interstitial cells. Spermatogenesis was absent and the interstitial cells augmented in a case of polyarthritis. In the remainder, including cases of scarlatina, sepsis, peritonitis and meningitis, there were preservation of spermatogenesis and no hyperplasia of the interstitial cells. Lastly, in six patients dying accidentally there were no increase in the interstitial cells and preservation of spermatogenesis in all.

Bouin and Ancel mentioned the occurrence of hypertrophy of the "interstitial gland" in persons with illnesses running a rapid course, such as pneumonia and certain forms of tuberculosis.

In an investigation of the testes of fifty-eight persons dying of acute illnesses of various sorts, Kyrle observed a proliferation of interstitial cells in all that showed marked parenchymal alteration. He concluded that the factor determining the occurrence of hyperplasia of the interstitial cells was an injury to the parenchyma sufficiently intensive or long lasting to produce at least cessation of spermatogenesis.

Undescended Testes.—When the testis remains undescended, its function is not usually preserved. As a rule it undergoes early atrophy with narrowing, sclerosis and atrophy of the tubules. In light of the data already presented, one should expect to find hyperplasia of the interstitial cells not uncommon.

Finotti reported sixteen cases of undescended testes. Atrophy was constant. All the testes were smaller than normal, with the exception of one, and the size of this was retained merely by virtue of exceedingly marked hyperplasia of the interstitial cells. Varying degrees of tubular atrophy, which was sometimes quite conspicuous, was present in all cases. The increase in the interstitial cells was constant. The cells were found singly, in groups and in rows between the atrophic tubules. The nuclei were relatively small. The cytoplasm contained fat, pigment and occasionally Reincke's crystalloids. In two cases the proliferation was extreme, with the cells in compact round masses traversed by numerous capillaries. The nuclei were always well preserved. Cells with two nuclei were not uncommon. Rarely, metaplasia (anaplasia) was seen. The intense proliferation and the masses of young cells with numerous blood vessels gave Finotti the impression of a proliferation like that of a beginning new growth. Invasion of the atrophic tubules by the interstitial cells was never observed.

Félizet and Branca, in their researches on ectopic testicles removed at and after puberty, made similar observations. Before puberty, interstitial cells were rare. However, in ectopic testicles removed after puberty, they found atrophy of the seminiferous tubules accompanied by an increase of the interstitial cells between the tubules to be the rule. The tubules showed varying degrees of atrophy and sclerosis, with the seminal lineage practically never complete. Interstitial cells were almost always increased in number. At times they replaced practically the entire stroma. They contained pigment, fat vacuoles and Reincke's crystalloids. Their topography was not fixed. They occurred individually, in islands, as rounded nodules, as cords between the tubules or as girdles around them. Their aspect was often epithelioid. Occasionally, they were seen in the walls of the tubules. This the authors interpreted as indicating an evolution in situ of the interstitial cells from the connective tissue of the tubular wall. (Compare this explanation with that of Spangaro.)

Grynfeldt, Truc and Guibert reported a case of ectopic testicle in which there was considerable hyperplasia of the "interstitial gland."

GRYNFELDT, TRUC AND GUIBERT'S CASE.—A 56 year old man underwent a suprapubic cystostomy for symptoms of prostatism. At operation a small soft testicle was found 2 cm. above the pubis and was removed. The other testicle was descended. Microscopically, the tubules of the removed testicle were seen to be profoundly modified. The epithelial lining was almost completely atrophied, and spermatogenesis was absent. The tubular walls were sclerosed, with enormous development of the collagenous coat. The tubular lumens were narrowed. Considerable collections of well vascularized chromophilic masses infiltrated the intertubular stroma, forming cords which insinuated themselves in the intertubular spaces, broad ridges which pushed the tubules back, and perivascular and peritubular collars. These collections were formed of cells identified with interstitial cells. The cells were polygonal, with round or oval nuclei containing one or two nucleoli. The cytoplasm was acidophilic and usually homogeneous, though occasionally it was granular. With higher magnification, the cytoplasm was seen to be hollowed by vacuoles of varying dimension, which at times filled the entire cell and gave it a foamy appearance. No Reincke's crystalloids were present, but a number of cells showed black granules when stained with iron hematoxylin. Large cells with multilobed nuclei or nuclei in amitotic division were seen. Actual mitoses were rare. Occasionally there were seen cells "invading" the tubular walls.

The authors expressed the belief that the amitoses, the nuclear monstrosities and the tubular "invasion" were indications of a possible precancerous growth. However, the observations of Spangaro of interstitial cells in the walls of the tubules in the hyperplasia of interstitial cells occurring in atrophic senile testes and those of Félizet and Branca in cryptorchidism hardly permit the finding of these cells in the tubular walls in hyperplastic states to be used as evidence of a precancerous state. Amitoses and nuclear monstrosities have also been observed previously in the more vigorous hyperplasias.

Pick, Simmonds, Koch, Kyrle and Stoppato also noted the frequent finding of marked hyperplasia of the interstitial cells accompanying the tubular degeneration occurring in undescended testes.

Pseudohermaphroditism.—Similarly, one would expect to find hyperplasia of the interstitial cells in pseudohermaphrodites in whom the testicular function is diminished or absent. The literature contains reports by Stroebe, Pick and de Josselin de Jong.

Stroebe's Case.—A 63 year old man who died of esophageal carcinoma presented external genitalia of normal appearance. The penis appeared normal, measuring 10.5 cm., and the urethral orifice was in the proper position. The scrotum was well developed, but there were no testes palpable. In the abdomen was found an elongated uterus with well developed round ligaments and tubes. On either side was a bean-shaped, grayish red organ which microscopically were seen to be testes. Each was enclosed in an albuginea. The tubules were degenerated and largely hyalinized, with their epithelium practically gone. The tubular lumens were considerably narrowed. The tubules were embedded in a richly developed interstitial substance containing numerous full blood vessels and consisting in the main of large polymorphous cells with round, oval or occasional spindle-shaped nuclei and well developed protoplasm containing fine brown-yellow pigment. This interstitial tissue surrounded the tubules or groups of them in bands of varying width. Many of the collections were sufficiently large to be visible macroscopically as islands of pigment cells the size of a pinhead.

Pick's Case.—A 38 year old "internal masculine pseudohermaphrodite" had atrophic testes, measuring 3.5 by 2 cm. The decrease in size was due to parenchymal atrophy. The markedly diminished tubules were embedded in, and largely overgrown by, a stroma containing groups, strands, nodules or regular diffuse sheets of interstitial cells which at times formed the only intertubular stroma. These cells were of epithelioid appearance, with vesicular nuclei and intensely pigmented cytoplasm. At times the cytoplasm contained vacuoles of varying size. Mitosis were not seen, despite the vigorous proliferation. No Reincke's crystalloids were present. The largest groups of cells measured about 1 mm. and were visible grossly.

De Josselin de Jong's Case.—A 42 year old "internal masculine pseudohermaphrodite" presented a large tumor in the left testicle. The right testicle was situated at the external inguinal ring and was reduced to the size of an acorn. Microscopically, the tubules were seen to be badly developed; spermatogenesis was absent. The intertubular stroma was increased and contained groups of interstitial cells. For the most part these groups were small, though one of them measured 2.5 mm. and was visible grossly. The details of this case with reference to the left testicle will be given later.

Local Conditions.—Hyperplasia of the interstitial cells of varying degree has been observed in various local conditions, such as long lasting compression of the cord, stricture of the vas, deferentitis and chronic disease of the bladder and prostate (Simmonds).

Experimental States.—In experimental states causing tubular atrophy, hyperplasia of the interstitial cells is also frequently noted. Kyrle subjected the testes of thirty-five dogs to roentgen irradiation. The exposure given to thirty-three was not sufficient to cause more than minimal changes. The testes were slightly reduced in size. The tubules were smaller, and the membrana propria was thrown in fine folds. The interstitial tissue was moderately proliferated. Two animals showed a more abnormal reaction. Their testes were reduced to one-half normal size. Microscopically, this was seen to be due to extreme atrophy of the tubules, which were much thickened and sometimes hyalinized. The interstitial substance was much increased, largely by virtue of an increase in the interstitial cells. Biopsy specimens were taken from one of these dogs after each of three successive exposures. A greater degree of parenchymal atrophy and of proliferation of interstitial cells was found with each successive exposure. Simmonds similarly noted atrophy of the specific elements followed by proliferation of the interstitial cells in testes that had been subjected to irradiation. Both authors observed that when the toxic effect of the roentgen rays was withdrawn, if atrophy of the parenchyma had not progressed too far, regeneration of the epithelium followed by a regression of the interstitial cells occurred. The authors concluded that the hyperplasia observed was secondary to, and compensatory for, the parenchymal destruction.

Experimental atrophy produced in different fashion by Bouin and Ancel resulted in identical changes. They observed that after the ligation of the vas in young rabbits the seminal tubules were poor in cells and contained no spermatozoa, even after four months, while the interstitial cells were well preserved and somewhat augmented. When ligation of the vas was accompanied by contralateral castration, after six months the testes were definitely smaller and the seminiferous tubules showed only a few spermatogonia, while the Sertoli cells were unchanged and the "interstitial gland" enormously developed. In from ten to twelve months the tubules were very shriveled, the Sertoli cells were degenerated and the testes consisted almost entirely of hyperplastic Leydig cells. The authors also induced states of chronic alcoholic and of chronic tuberculous intoxication in rats, with resultant hypertrophy of the "interstitial gland." Bleeding of rats or destruction of the adrenal capsule had the same effect.

Summary.—It is seen, then, that in any condition, local, general or experimental, in which cessation of spermatogenic activity and tubular atrophy occur, hyperplasia of the interstitial cells may secondarily ensue. This secondary hyperplasia may be so marked as to form almost the entire stroma and even to maintain the size of the testicle despite marked tubular atrophy. Further tubular atrophy may be caused by pressure of the greatly augmented interstitial cells. The primary and initiating factor, however, is the parenchymal destruction. At times the appearance of beginning new growth is suggested by the more vigorous hyperplasia, with marked tubular atrophy, anaplasia, bizarre nuclear forms and even apparent invasion of the tubular wall. It is to be remembered in this connection that all these features also accompany the less vigorous hyperplasia in which no question of possible new growth exists and hence in themselves cannot be used as criteria to distinguish one from the other. Moreover, in practically all cases the proliferation can be seen to be intertubular, involving the entire testicle diffusely and uniformly rather than seeming to originate from a single focus and expanding centrifugally from there, as one would expect to see in the case of new growth. The proliferating cells retain for the most part the characteristics of the mother cell. They are polymorphic cells with abundant acidophilic cytoplasm and relatively small nuclei. Various inclusions (lipoid droplets, pigment, refractile granules, etc.) may be observed in the cytoplasm, though these changes are not constant.

TUMORS ARISING FROM THE INTERSTITIAL CELLS

The first reference to tumors derived from interstitial cells was made by Waldeyer in 1872. He spoke of tumor formations arising from the perithelial cells in the brain, lymph vessels and testes, forming soft neoplasms consisting of vascular plexuses, the individual vessels of which had a covering of epithelial cells which assumed the arrangement of anastomosing strands. The individual cells he described as being rich in protoplasm, containing fine dark granules and having pseudopods. He identified these with Leydig's cells. To this type of lesion he gave the name plexiform angiosarcoma. He specified that in the testis such a growth might readily be confused with carcinoma.

Hansemann in 1895 next referred to tumors which he believed to arise from the cells of Leydig. Practically no description of the component cell is given, except that the tumors described were composed of large cells surrounded by a netlike intercellular substance, the cells markedly resembling interstitial cells. Such growths, he said, might resemble a sarcoma or a carcinoma. An illustration is provided.

Later authors who interested themselves in the subject of interstitial cell tumor seem to be agreed that the tumors described by Waldeyer and Hansemann are not to be included in this category. Hansemann himself, in discussing Waldeyer's plexiform angiosarcoma, stated that the description was doubtless too far reaching and would probably include both angiosarcoma and interstitial cell tumor, Waldeyer having been misled into including interstitial cell tumor in this classification because of the intimate relation of the tumor cells to the vessels. And, he added, there is no real surety that Waldeyer observed actual interstitial cell growths, as the relation of the vessels was closer than would be present in growths of this type. Langhans similarly was unable to accept Waldeyer's conclusions. Krompecher identified the tumors described by Hansemann with his group of large cell alveolar sarcomas (really carcinomas), and Debarnardi was in accord with this view. Chevassu, in his treatise on testicular tumors, in which he described both the seminoma and the interstitial cell tumor, stated that the growths described by Waldeyer as plexiform angiosarcomas were probably seminomas, and that although Hansemann's description was summary, the illustration in the text left little doubt that he likewise was dealing with seminomas. The cellular constituents of the lesions described by Hansemann, he stated, were not like those of interstitial cells. The nuclei were larger and the cytoplasm less abundant, with an absence of inclusions. Ewing stated that the descriptions of Waldeyer and of Hansemann were brief, suggesting the possibility of interstitial cell tumor but hardly establishing the fact. He referred to certain cases of his own in which portions of the tumors resembled Hansemann's tumor but the growths were diffuse carcinomas occurring as part of teratoid growths. Masson and Sencert, who later reported a case of interstitial cell tumor, were in accord with the opinion that the tumors referred to in reality arose from cells of the seminal line. Panà similarly concurred, and Peyron criticized the classification of these growths as interstitial cell tumors as errors in diagnosis.

In 1906 Chevassu described the seminoma and identified Waldeyer's plexiform angiosarcoma and Hansemann's interstitial cell sarcoma with it. He then described a tumor with characteristics isolating it from all other testicular growths. It was composed of cells resembling markedly the cells of Leydig and different than those of the common round or polygonal cell tumor.

CHEVASSU'S CASE.—A 27 year old man, with his left testicle in the inguinal canal, several years previously had been operated on for hernia on that side, and in the ensuing months a tumor had appeared under the scar. This had gradually enlarged to the size of a fist. The mass was removed at a second operation and was found to contain the left testicle, which was enlarged to the size of a small hen's egg. The tumor was quite hard and had apparently completely replaced the testicle. No trace of normal testicle was apparent on section. The sectioned surface was seen to consist of reddish yellow lobules divided off by paler spans of what proved to be connective tissue. Microscopically, the reddish yellow lobules were composed of masses of large polygonal cells with voluminous, deeply tinted cytoplasm containing deeply staining granules and numerous vacuoles, which at times riddled the cytoplasm. No Reincke's crystalloids were seen. The nuclei were spherical and clear and in general compressed toward one border of the cell. Traversing the cellular masses were adult capillaries, frequently in close contact with the tumor cells. The entire tumor was limited by a shell of fibrous tissue in which were found a few flattened, thickened, sclerosed, residual seminiferous tubules. Histologically, the lesion seemed benign, and twenty-two months after operation the patient was alive and well with no evidence of recurrence.

This tumor, according to Chevassu, was a neoplasm of the primitive interstitial cells, the first to be described. The similarity of these cells to interstitial cells, with their voluminous, highly staining cytoplasm, containing deeply staining granules and vacuoles, their small clear nuclei and their frequent close contact with capillaries, was as apparent as their dissimilarity to the cells of tumors derived from seminal epithelium. The absence of Reincke's crystalloids and other secretory products he deemed of no importance. The rapidity of proliferation did not furnish sufficient time for the edification of these products. Authors studying the problem of interstitial cell tumor since have all accredited the authenticity of this tumor's origin from interstitial cells.

Kaufmann, the following year, described the testes removed from a 30 year old man, both of which were the seat of similar changes, and in 1908 he reported on the testicle removed from the brother of this patient, a man of 34.

KAUFMANN'S CASE 1.—The patient was mentally retarded, though strong physically. Both testes were in the scrotum and presented similar changes. One measured 9 by 6 cm., and the other was slightly smaller. The shape of the testicles was retained. The consistency was firm, with a grating on sectioning. Grossly, the tumor was broken into irregular, plump, brownish red lobules by connective tissue. Microscopically, the parenchyma was reduced to a few scattered subalbugineal groups of atrophied tubules. Proliferation of the interstitial cells, such as is ordinarily found in cases of diffuse hyperplasia, was absent from between these subalbugineal tubules, which appeared as though pushed outward by the developing tumor mass within. The tumor tissue consisted of netlike strands, nests and masses of large epithelioid cells in intimate relationship to fine vessels which subdivided the large cell masses. The arrangement and cell type were very suggestive of liver, adrenal cortex or alveolar tumor of the carotid gland. The individual cells were polymorphous, mostly polyhedral. The nuclei were round or elliptic and about the size of a red blood cell, though some were twice as large. The network of chromatin was sparse. One or two nucleoli were present. Occasionally multinucleated cells were seen. The protoplasm was granular, with many vacuoles. Many cells contained fine round, yellow brown pigment granules, while others seemed diffusely pigmented. The pigment was similar in nature to that occurring physiologically in interstitial cells. The fat content of the cells was rich, as evidenced by the presence of numerous large and small droplets without destruction of the cell. This gave the cells a weblike appearance on extraction of the fat. Reincke's crystalloids were not seen.

KAUFMANN'S CASE 2.—The testicle of the brother of the preceding patient was fully descended, weighed 150 Gm., and was 9 cm. long. Macroscopically and microscopically, it was similar in all respects to the brother's, except that the tubular crests were lacking. The other testicle in this patient, which was left in situ, was voluminous and quite likely, Kaufmann stated, the seat of similar changes.

Kaufmann stated that the growths were probably benign, because, though present for many years, there had been no invasion of the tunica or epididymis. However, he did not make a definite statement, because he considered the polymorphism of the cells to be suggestive of a malignant process.

The character of the cells in these cases is obviously fundamentally similar to that of the cells of Leydig. Chevassu, who had an opportunity to study the material in Kaufmann's cases, found the cells quite like those in his own. The appearance of the cells and of their protoplasm and nuclei were, he stated, similar in all specimens examined.

Dürck, in the same year, described four cases in which there was an enormous increase in interstitial cells.

DÜRCK'S CASE 1.—A vigorous 25 year old carpenter died of a fractured skull sustained in a fall from a building. Both testes were in the scrotum but were remarkably small, measuring 1.8 by 1 cm. and weighing 7 Gm. with the epididymis. Their color was dark brown. The tubules were extraordinarily reduced, their tunica propria thickened and hyalinized, their lumens narrowed and their epithelium atrophic, with barely a sign of spermatogenesis. Between the atrophic tubules were seen broad beds of large polygonal cells with abundant cytoplasm and round vesicular nuclei with definite nucleoli. These cells made up the bulk of the testicle.

DÜRCK'S CASE 2.—A 64 year old man died of purpura.. The testes, which were brown and about the size of a hazelnut, were in the peritoneal cavity. The tubules were again seen to be reduced in number, their walls thickened with concentric layers of fibrous tissue and their lumens reduced, with few epithelial cells. The interstitial cells between the tubules were greatly increased and large, their nuclei being variable in size and the nucleoli large and dark. The cytoplasm contained abundant sharply refractile fat vacuoles and abundant, though irregularly distributed, light brown pigment.

According to Dürck, the picture presented was suggestive of polymorphous pigment cell sarcoma.

DÜRCK'S CASE 3.—A powerfully built man of 45, who died suddenly of a heart attack, was found to have aortitis and disease of the coronary artery at postmortem examination. Both testes were in the scrotum and were small and dark. The seminiferous tubules were reduced in number and size, and their tunica propria was thickened and hyalinized. The major portion of the preparation was composed of intertubular masses of interstitial cells rich in fat vacuoles and in irregularly arranged pigment.

DÜRCK'S CASE 4.—A 43 year old man, who died of tuberculous pachymeningitis, had contracted gonorrhea thirteen years prior to his death. Two years later he received a heavy blow on the scrotum, after which the left testicle diminished in size, while the right became larger for a time and then remained constant. The right testicle was larger than a walnut. The seminiferous tubules had almost entirely disappeared. Only occasionally was a small calibered tubule lined by a single layer of epithelium seen. Practically the entire preparation consisted of cell-poor bridges of fibrillary tissue with the intervening spaces entirely filled by polygonal cells with vesicular nuclei. The cells in this case were somewhat smaller than those in case 1. Atypical mitoses were present.

To Dürck, the picture resembled that of a sarcoma. The left testicle was the seat of a diffuse fibrous orchitis in which interstitial cells were not seen.

Dürck was of the opinion that in his cases the tumors were of a special form, even though the testes were smaller than normal. Evidence for their neoplastic nature, he said, is seen in the fat degeneration in case 3, in the pigmentation in cases 2 and 3 and in the variability of cell form and the atypical mitoses in case 4. The proliferation of the interstitial cells was primary, he added, and the tubular atrophy secondary. This might occur in descended as well as in ectopic testes. In cases 1 and 3, there was no etiologic factor that might produce primary tubular atrophy.

On analysis of the material presented, one sees that the picture found is much more closely akin to hyperplasia than to neoplasia. Except in case 4, the testes were all considerably smaller than normal. Though reduced in number, tubules were present throughout the testes in the first three cases, with proliferation of the interstitial cells being essentially intertubular, rather than pushed back to the subalbugineal region by an expanding lesion. This is the topography seen in cases of hyperplasia as compared to that seen in Kaufmann's cases, in one of which no tubules were present, while in the others they were limited to a few subalbugineal groups with no interstitial cells between them, or as compared to that in Chevassu's case in which only a few tubules were found in the limiting fibrous shell. The fat and pigment found were, of course, cytoplasmic inclusions, which are normally present. The variability of cell form and the atypical mitoses have been seen in the more vigorous hyperplasias described. In case 2 an etiologic factor for primary tubular atrophy and secondary hyperplasia of the interstitial cells was present, namely, cryptorchidism. In cases 1 and 3 there was no apparent etiologic factor for the parenchymal atrophy. In case 4 death was due to tuberculous pachymeningitis. Whether tuberculosis was present in the other organs is not stated. Cachexia due to tuberculosis as well as testicular atrophy due to gonorrhea are agents which can produce secondary hyperplasia of the interstitial cells. However, the testicular injury with its immediate sequel of testicular alteration is also of interest because of the alleged relationship of injury to testicular tumor. Moreover, the growth in this case, by its gross and microscopic characteristics, more closely approaches an actual neoplasm. It was larger than the growths in the other cases, being almost the size of a normal testicle. The tubules for the most part had disappeared. The cells were less typical, and it is in this case that the atypical mitoses were seen. The question of neoplasm in this case must therefore remain sub judice.

Thus there remains one case of questionable neoplasia of the interstitial cells. The conditions in the other three cases can hardly be designated as anything but hyperplasia, though because of the absence of any evident etiologic factor for the primary tubular atrophy in cases 1 and 3 the possibility that hyperplasia of the interstitial cells may arise as a disease sui generis must be kept in mind. Also, as suggested by Peyron, one must consider that the presence of a hyperplasia of these cells may serve as a soil for the development of an actual neoplasm.

The next report is that of Stoppato, who in 1911 described three growths which he designated as interstitial cell tumors.

STOPPATO'S CASE 1.—A 38 year old man had a testicular tumor which developed painlessly over the course of a year. It measured 8 by 6.5 by 2 cm., and was grayish with a central yellow area of softening. No normal parenchyma was left, though beneath the albuginea were the remains of some seminal tubules, with thick, hyaline walls. The tumor tissue was composed of cell strands of from two or three to twenty or thirty cells in width separated by a fibrous stroma containing a few small cells. The tumor cells were large (from 14 to 18 microns), round or polygonal. The protoplasm stained violet-rose with hematoxylin and eosin, was irregularly granular and contained numerous vacuoles, giving the cells a foamy appearance. The nuclei were also large (from 8 to 14 microns), rich in chromatin and round, polygonal or oval, with at least one nucleolus. Mitoses were seen. Necrotic areas were present. The cells contained no pigment or crystalloids, but the protoplasm was rich in glycogen. Peripherally, between the residual tubules, were seen groups of from three or four to thirty or forty true interstitial cells. They differed from the tumor cells in that they were relatively rich in protoplasm, their nuclei were vesicular with little chromatin, the nucleolus was more sharply defined and the protoplasm was free from glycogen. Transitional forms to cells with nuclei richer in chromatin were observed. However, these transitional forms still were free from glycogen and showed no mitotic figures.

STOPPATO'S CASE 2.—A 26 year old man, whose clinical history was not available, had a testicle which measured 9 by 6 by 4 cm., was grayish red and elastic and was divided into prominent lobules. The only trace of testicular tissue present was some atrophic tubules beneath the albuginea. The tumor cells were arranged in strands separated by an interweaving cell-poor stroma, which was richer in cells than that in case 1, the cells being mainly lymphocytes. The tumor cells were large (from 13 to 15 microns). The protoplasm was relatively sparse, clear and vacuolated. The nuclei were also large (from 9 to 12 microns), with scanty chromatin, and usually contained one nucleolus. Mitoses were observed. No pigment, crystals or crystalloids were seen. Again the cells were rich in glycogen. Between the atrophic tubules were groups of true interstitial cells—large polyhedral cells with abundant rose colored cytoplasm lacking glycogen and eccentric vesicular nuclei.

STOPPATO'S CASE 3.—A tumor occurred in a fully descended testicle that had undergone tumefaction after an injury suffered two months previously. It was firm, measured 8 by 5 by 3.5 cm. and showed a lobular structure on cut section. It was gray or grayish red. An occasional atrophic seminiferous tubule was seen beneath the albuginea. Apart from this no trace of testicular parenchyma remained, the tumor consisting of cellular tissue divided into strands by a cell-poor stroma. The tumor cells were large (from 14 to 18 microns), and the protoplasm pale red, finely granular or water clear. The nuclei were large (from 8 to 12 microns) and rich in chromatin and contained from two to four nucleoli. Mitoses were observed. The cytoplasm contained no pigment, crystals or crystalloids, though much glycogen was present. In this case no normal interstitial cells were seen between the atrophic seminiferous tubules beneath the albuginea.

The cell type found in these three tumors differs both from that found in the cases reported by Kaufmann and Chevassu and from the interstitial cell. The cytoplasm was scanty, without inclusions of any sort, and contained much glycogen. The nucleus was large, filled the greater portion of the cell and was rich in chromatin. Moreover, in the first two cases real interstitial cells were observed between the residual tubules, these cells differing markedly from the actual tumor cells. Stoppato himself, in analyzing his cases and comparing them with those of Chevassu and Kaufmann, admitted that differences existed and that the resemblance of the cells of his cases to interstitial cells was not as great as that of the cells in the cases of the two aforementioned authors. That his concept of the nature of the lesion he observed was not quite clear is further evidenced by the fact that he included in his discussion the cases of Waldeyer and Hansemann as cases of true interstitial cell tumor. He stated further that by using Debernardi's classification his cases would fall into the group of large cell malignant tumors, though they were not absolutely identical with them. It has been shown that this group of tumors is derived from spermatogonia (seminomas).

Doubtless the growths in these three cases are to be classified as large cell testicular tumors or seminomas rather than as neoplasma derived from the interstitial cells. Further support is given this view by Frank, who allied Stoppato's material with large cell testicular tumors derived from the layer of spermatogonia of the tubuli contorti. Ewing's description of embryonal cell carcinoma of the testicle is practically identical with the appearance of these growths. He described under this heading lesions composed of large round or polyhedral cells, rich in glycogen with hyperchromatic nuclei. The stroma, similar to that in Stoppato's cases, was scanty, or strands of lymphoid tissue might be prominent. Finally, Peyron stated, after having had the opportunity to study Stoppato's original preparations (which were placed at his disposal by Professor Wegelin, associated with the same institute as Stoppato), that the tumors reported were seminomas. The view held by Professor Wegelin, Peyron added, was in accord with his.

PEPPERE'S CASE (1922).—An ovoid, encapsulated, soft, yellow tumor of the testicle, the size of a hen's egg, was removed from a 1½ year old child. The tumor had grown slowly from birth. No seminal tissue was seen. The neoplastic tissue was uniform and was composed of cells with uniform morphologic characteristics. The cells were compressed like "tile paving" and were interrupted solely by turgid capillaries. The individual cells were polyhedral or polygonal, with abundant clear cytoplasm. The nuclei were large and vesicular, with sparse chromatin filaments.

Peppere's interpretation was that the lesion was a sarcoma derived from the cells of Leydig analogous to the hypertrophy that occurs in cryptorchidism. Though the description given is too summary for definite conclusions, it leaves the impression that the component cell is more closely allied to that of Debernardi's large cell tumors (seminoma of Chevassu or embryonal carcinoma of Ewing).

The next contribution was made by Masson and Sencert in 1923.

MASSON AND SENCERT'S CASE.—A 52 year old mason, with an irrelevant previous history, had his right testicle removed for a heavy swelling of several months' duration. The tumor was hard, grayish with blue areas and quite vascular. It measured 8 by 4 by 4 cm. and was completely enclosed by the albuginea. Atrophic, compressed, thickened seminiferous tubules were present in the subalbugineal region, apparently pushed toward the periphery by a tumor arising in the depths of the testicle and expanding outward. Separating the tumor from the subalbugineal parenchyma was an imperfect fibrous capsule without precise limits, invaded and dissociated in areas by neoplastic tissue. A rare interstitial cell was found between the tubules immediately under the albuginea. The tumor tissue was formed of interlacing, anastomosing cellular cords of irregular thickness, enveloped by a fine connective tissue sheath in which were numerous capillaries. The arrangement resembled the crescents of the seromucous salivary glands. Centrally the tumor was necrotic and hemorrhagic. The tumor cells were large and polymorphous and intensely though unequally acidophilic, some being colored *en masse* and others finely granulated by eosin. Some cells were vacuolated and some were practically excavated. Still others were strewn with highly colored refractile granules similar to secretory granules. The nuclei were round or oval, voluminous, and central or eccentric and were always situated in a dense cytoplasmic region. They contained fine chromatin granules and one or two nucleoli. Mitoses were observed, ordinary and pluripolar.

Four years later the patient returned with a metastatic mass in the right groin. He died of bronchopneumonia twenty-six days after extirpation was attempted. At autopsy there were found in addition to the large recurrent mass in the right groin, which had penetrated the femur, numerous metastases in the lungs and a large metastatic gland at the root of the aorta. The metastatic tumors were reddish, partially hemorrhagic and spotted with yellow necrotic areas. Microscopically, all were identical. Where not necrotic, they were compact and exceedingly vascular. The cells formed mosaics with innumerable capillaries. The appearance was similar to liver or to adrenal cortex. The tumor cells when dissociated were spherical. Most contained minute grease drops in the periphery; some were quite loaded with fat. A few cells had feeble amounts of glycogen, but never in abundance—different, according to the author, than in the seminoma.

The cytoplasm was acidophilic and granular, and the nuclei were spherical. In the palisade cells along the sinusoidal vessels the nuclei were always on the far side. The nuclear texture was finely reticulated. One or two nucleoli were present in each cell, and mitotic figures were numerous. These cells, Masson stated, differed more from interstitial cells than those of the original tumor; so much so, that their nature would be difficult to affirm without study of the original tumor. He stressed the resemblance of the picture presented in these metastatic foci to that of an endocrine gland.

The resemblance of the cells composing this tumor to interstitial cells is striking despite the absence of pigment or crystalloids. This absence has already been encountered in Chevassu's case. Although the lack of this very characteristic feature of interstitial cells makes it difficult to state with complete assurance that this tumor originated from these cells, the polymorphism of the cells, with their abundant, highly colored cytoplasm containing lipoid and highly refractile secretory granules, makes this quite likely. Cells derived from epithelial lineage lack the size and marked colorability of the cytoplasm of these cells. The arrangement of cells to resemble liver or salivary gland has also been seen in previous cases. Oberndorfer, Panà, Caudière and Peyron apparently all agree as to the derivation of this neoplasm from the cells of Leydig. The obvious malignant nature of the growth segregates it somewhat from those reported by Kaufmann and Chevassu but certainly does not militate against its interstitial cell origin.

De Josselin de Jong's Case (1926).—An intra-abdominal tumor the size of a child's head was found arising from the left intra-abdominal testicle of a 42 year old "internal masculine pseudohermaphrodite." On section, the tumor was in most places soft, bloody and necrotic. The small, well preserved areas were gray-yellow or brownish. Microscopically, the greater portion was amorphous, edematous and somewhat bloody, with granular masses showing strong necrosis. Small islands of fairly well preserved cells were seen, though the cells themselves showed many signs of degeneration (fat droplets, vacuoles and hydropic swelling). This gave the tumor an irregular structure. The cells were often grouped to form a netlike arrangement of strands. At the edge of the growth was a connective tissue stroma in which the tumor cells lay in bands, rows or irregular groups. The cells were better preserved here and were polymorphous. The protoplasm was variable, and in some cells abundant and somewhat granular, with large or small vacuoles. The nuclei were of variable size, mainly round, staining clearly. With sudan III many of the vacuoles in the protoplasm were seen to be fat globules. The author stated that in many areas the cells resembled interstitial cells. The tumor was rich in blood vessels, which were thin walled, consisting of only one layer of endothelial cells. The tumor cells seemed to cling to the blood vessels or were limited by them. No pigment or crystalloids were found. No mitotic figures were present. The growth was malignant. De Jong received a communication from the patient's physician that metastases had developed but that the patient was now visiting some faith healer for treatment. The tubular atrophy and hyperplasia of the interstitial cells in the right testicle have already been described.

In this tumor degenerative processes were so active and prominent that it is difficult to draw any positive conclusions as to its genesis. The author expressed the belief that the growth was a malignant tumor of sarcomatous nature arising from the interstitial cells of the testicle. He discussed the possibility of malignant hypernephroma but dismissed it because of the hemorrhagic nature, the widespread necrosis, the polymorphism of the cells and the cell degeneration. Though there are some resemblances between the cell type seen here and that of other reported cases, on the whole they are not marked, consisting in large part of the polymorphism of cell and the abundant fat vacuoles in the cytoplasm. In view of the rapid proliferation and degeneration present even in the better preserved portions, it is presumptive to interpret these as characteristics of the cell rather than of the proliferative and degenerative process. The illustration in the text resembles more a rapidly growing and degenerating embryonal tumor than one of interstitial cell origin and differs from the accompanying illustration of the proliferating interstitial cell foci in the other testicle. Also, the marked cell degeneration, the hemorrhage and necroses seen here have not been observed in the other cases reported.

VILLATA'S CASE (1928).—A testicular tumor was found arising in the descended right testicle of an underdeveloped man of 22. It was more than twice the size of a normal testicle. The opposite testicle was in the inguinal canal. Potency was retained. The patient had, in addition, hypospadias and bilateral inguinal hernia. The specimen consisted of a central necrotic portion and a peripheral ring of tumor tissue. The residual tubules were sparse and widely separated, showing absence of spermatogenesis and alterations of progressive atrophy. There were two types of tumor tissue present. Some areas were composed of large round cells with complete boundaries and a clear cell body containing large round or oval nuclei rich in chromatin. Between portions of this character were other areas of cells disposed in cords of varying size, occupying large uninterrupted areas. Tumor tissue of this second type prevailed. These portions were composed of polyhedral, ovoid or bizarre cells. The cytoplasm stained vivid rose with hematoxylin and eosin and was finely vacuolar. The vacuoles proved to be lipoid droplets. No lipochrome was found. The nuclei were small, irregular and less intensely colored than those of the large round cells.

Obviously this tumor was of a teratoid nature, the only interest in which is to show that neoplasia of the interstitial cells may occur as a derivative of teratoma testis.

SLANINA'S CASE (1930).—A tumor the size of a hen's egg developed over a period of eight years in a man who was 45 at the time the tumor was removed. It was 10 cm. in length, was hard and weighed 94 Gm. On section, it was bluish except near the periphery, where it was golden tan. The cells were round, and the protoplasm had numerous vacuoles. Many capillaries of one layer of endothelium were present. No seminiferous tubules were seen.

Though Slanina considered this a tumor of the interstitial cells, the briefness of his report renders impossible any definite statement as to its nature and origin. It seems, however, from the little given that the constituent cell bears not too close a resemblance to interstitial cells. The illustration in the text also is less suggestive of interstitial cell tumor than of seminoma.

The final recorded case is that of Panà, who in 1931 described a specimen obtained from autopsy material. Only little clinical data were available.

PANÀ'S CASE.—An ovoid, white, firm tumor, measuring 6.2 by 3.1 by 2.9 cm. and weighing 28 Gm., was found in the fully descended testicle of a 16 year old boy, who died of sepsis following acute otitis. The opposite testicle was undescended. Grossly, the tumor was seen to be divided into a peripheral, hard, whitish-gray cortical zone and a central zone of ocher with darker spots. The central zone projected irregularly into the cortical zone. Microscopically, the cortical zone was seen to be composed of the tunica albuginea, no longer individualized but augmented by large bundles of connective tissue fibers. Toward the internal aspect these were less compact. The central zone was made up of interlacing cell strings, having no regular arrangement. The cells were usually oblong or oval; some were polyhedral, and others, irregular or cubical. They were clear and vitreous and contained vacuoles that did not stain with the ordinary stains. The nuclei were round, rich in chromatin and medium sized. The cytoplasm in some cells contained brown-yellow pigment granules and more rarely, spherical acidophilic granules. In this central region the tissue was poor in connective elements, the stroma consisting only of reticulated pericellular fibers. In the zone of transition from the central to the cortical region, the stroma was abundant. In this intermediate part, small atrophic residues of seminiferous tubules were seen. No normal parenchymatous areas and no areas of distinct necrosis or containing diffuse hemorrhage were observed.

One has here a lesion of quite characteristic cellular components, although de Bary questioned that it was a neoplasm rather than merely advanced hyperplasia. However, he offered as evidence only the statement that tumefaction is unknown in a descended testicle when the other is undescended. That this is not so has already been seen, even in a case reviewed here (Villata's case). The architecture seen is that of a neoplasm, the tumor proper (central zone) being devoid of parenchymal elements which exist only in the subalbugineal region (transitional zone), as in a lesion expanding outward from a central focus. This differs from the picture encountered in the ordinary hyperplasias, and, as a matter of fact, from that present in the opposite testicle, which was reduced in size, weighing 3.5 Gm. The parenchyma was greatly reduced; the few residual tubules were small in volume, with the lumen either obliterated or narrowed to a small slit. Seminiferous cells were scarce. The connective stroma was proliferous, consisting of broad bundles crossing the whole organ radially. In the stroma the interstitial cells were abundant, forming small nodules in some areas.

THE INTERSTITIAL CELLS IN ANIMALS

Both hyperplasia and neoplasia of the interstitial cells have been reported in animals. Normally the degree of development of interstitial cells varies with the species and the nutritional state of the animal. In the boar, cat and mole they are numerous; in the elephant, less so. In the marmot they are absent during the period of winter sleep, but with resumption of activity they become almost as numerous as in the boar (Hansemann).

Hyperplasia of interstitial cells in cryptorchid horses has been reported by Pallaske and in cryptorchid rabbits by Bouin and Ancel. Experimentally, hyperplasia of the interstitial cells has been produced by Bouin and Ancel in rabbits by ligation of the vas with or without contralateral castration and in rats by chronic intoxication with alcohol or tuberculous toxin. In hybrid birds (hybrid of peacock rooster and guinea-hen) immense proliferation of the interstitial cells with relegation of the semen-forming elements to the background was reported by Poll.

Kunze reported the occurrence of lesions which he described as interstitial cell tumors in twenty-three dogs. These occurred in the atrophied testes of old dogs, were often multiple and bilateral and consisted of small nodules within and usually just beneath the albuginea of the testis, which was never enlarged. The nodules were yellow-white in contrast to the darker parenchyma. The larger ones showed hemorrhagic degeneration. They were enveloped by a capsule of connective tissue and were penetrated by a well formed capillary network. Connective tissue was scarce. The average nodule was the size of a pea; larger ones up to the size of a cherry were formed by a conglomeration of the smaller nodules. Atrophied seminiferous tubules were compressed between the growths. The nodules were composed of cells closely resembling interstitial cells. They were polymorphous, with granular cytoplasm filled with vacuoles. The lipoid stained with scarlet red, at times in quantities filling the entire cell. In four animals pigment was present. The nuclei were round or oval with one nucleolus.

These lesions were interpreted by the author as interstitial cell tumors. However, their multiplicity, bilaterality and small size, in addition to what has already been seen of hyperplasia in man, leave one reluctant to accept them as anything but node-forming hyperplasia. This view is fortified by Pallaske, who observed identical changes with a high degree of regularity in the atrophic testes of senile dogs. As long as spermatogenesis persisted, only a few interstitial cells were seen. With cessation of spermatogenesis and atrophy of the tubules, these lesions made their appearance. He described the pathogenesis of these nodules from strands of several layers of interstitial cells surrounding an atrophic tubule or tubules, which atrophied further and finally disappeared with further growth of the cells, leaving a new nodule. Moreover, he added, in dogs approaching senility, nodelike hyperplasias of the interstitial substance are a common finding in many organs (liver, spleen, pancreas, thyroid and adrenal gland). Using only healthy dogs, Pallaske performed complete autopsies and examined all the organs for analogous nodelike hyperplasia of the interstitial tissue. He found nodular hyperplasia of the interstitial cells in the testicles of thirty-one of one hundred and seven dogs and nodelike hyperplasia of the interstitial substance in other organs in seventy-one of the dogs. In twenty-eight of the thirty-one dogs with testicular nodelike hyperplasia, hyperplasia of interstitial substance was present in the other organs as well. He concluded that the testicular lesions observed by Kunze and himself were not real tumors but were rather analogous to the hyperplasia of interstitial cells observed in the testes of cachectic men. As a contrast, he then offered a case of actual interstitial cell tumor arising in the testes of a horse.

PALLASKE'S CASE.—Both testes were much enlarged and moderately firm. The left was 31 by 17 cm. and weighed 8 Kg. The right weighed 2 Kg. The structure of each testis was the same. The parenchyma was replaced by tumor tissue except in an occasional small area, which grossly was gray. These areas contained atrophic tubules with hyaline basement membrane embedded in broad bands of tumor tissue. The tumor tissue itself was composed of polygonal cells, rich in protoplasm and with chromatin-poor nuclei, often eccentrically placed. Mitosis were observed. The protoplasm stained well with eosin. In most cells the protoplasm contained finely granular yellow-brown pigment, which remained yellow-brown when the cells were stained with scarlet red. No clinical history was available except that there were no grossly obvious metastases. It was not known whether there was local involvement of the lymph nodes. Structurally, the tumor seemed malignant, though it had not invaded the tunica.

The author was of the opinion that the picture resembled a polymorphous sarcoma derived from the interstitial cells. Little comment is necessary except that the malignancy of the lesion is not established.

Interstitial cell tumor of the testicle was reported by Ball in two dogs.

The first tumor was found in an adult dog. The testicle was four times normal size. On section, the tumor was homogeneous and was surrounded by a fine fibrous shell, which pushed back the seminiferous tubules, the majority of which were in a state of involution. The neoplastic elements were grouped in perivascular collars, which attained considerable size. Elsewhere the vascular axes were rare, the tumor cells being arranged in extensive cellular sheets. The cells were irregularly oval or polyhedral. The nuclei were small, ovoid or spherical, with a delicate reticulum. The perinuclear zone was usually homogeneous or finely granular. Multiplication was slow, by amitoses, and was often incomplete. Occasionally plurinucleated cells were seen. Degeneration was observed in the regions of the diffuse cellular sheets. There the cells were smaller, and cytolysis, karyolysis and pyknosis were found. Granular masses of disintegrated cells were seen. The cytoplasm of the cells showed a more or less generalized alveolar architecture, and this Ball offered as evidence of their origin from interstitial cells. In some areas the cellular elements were more voluminous.

the appearance suggesting fat cells at times and cells of a glandular acinus at others.

The second tumor occurred in the testicle of an old dog. The tumor was as large as that in the first dog, and the histologic structure was identical, though not as clear because of the presence of numerous hemorrhages.

Peyron, in discussing these tumors, stated that they indubitably arose from the interstitial cells of the testicle. He offered no specific differentiating features, though he did stress the difficulty in distinguishing interstitial cell tumor from seminomas in diffuse sheets. Despite the assurance of Ball and Peyron as to the validity of origin of these lesions from the testicular interstitial cells, the histologic description offered is too cursory to warrant any definite conclusion. The illustration in the text, however, is very suggestive of interstitial cell neoplasm.

REPORT OF AUTHOR'S CASE OF INTERSTITIAL CELL TUMOR OF THE TESTICLE

A 35 year old man was admitted to the hospital with the complaint of a protuberance in the right groin of two months' duration and one in the left groin, which appeared shortly thereafter. Cough and work made these protrusions more prominent. Exertion caused pain in the right groin. The patient also stated that his left testicle was considerably enlarged, having been so for fifteen or twenty years. The right testicle was somewhat small and had not grown at all in size in this period.

Potency was intact, but though the patient had been married for ten years there had been no children. Examination of a condom specimen eight years before his admission was said to have revealed live spermatozoa.

The patient had come to the United States from Poland twenty years previously. His habits were regular. The medical history was irrelevant. He had injured his nose and lacerated his upper lip twenty years before in a fall from the roof of a porch, but he said that he had not injured his testicles at that time. Eleven years later a nasal operation had been necessary to relieve obstruction. The systemic history was unimportant. The patient said that he had never had venereal disease or any symptom of it. The family history was noncontributory.

Physical examination revealed a well nourished white man of 35, who did not appear ill. The habitus was masculine, and the secondary sex characteristics were normal. The head was normal, except for the presence of pyorrhea and dental caries. No nodes, masses or abnormal pulsations were present in the neck. The heart and lungs were normal. Abdominal examination revealed only small indirect inguinal hernia bilaterally. The skin, extremities and osseous, lymphatic, arterial and neurologic systems were normal. Rectal digital examination revealed only a moderately enlarged prostate, especially the left lobe. The right testicle was small and insensitive. The left was twice normal size and was firm and solid. Its epididymis was slightly enlarged. Both testes were fully descended.

Urinalysis gave negative results. The blood pressure was 118 systolic and 78 diastolic. Hormonal studies were not made.

A modified Andrew's hernioplasty was performed bilaterally, and orchidectomy was done on the left side. The postoperative course was entirely uneventful. Both wounds healed by primary union, and the patient was discharged on the fourteenth postoperative day. The pathologic diagnosis, made by Drs. Klemperer and Otani, was interstitial cell tumor of the testicle. Because of the possibility of malignancy, even though not warranted by the clinical course and histologic picture, a course of radiotherapy was administered to the pelvis, the mediastinum and the spine for three months after the patient's discharge.

The results of the pathologic examination follow: The testicular mass, stripped of its appendages, measured 6.5 by 6 by 3.5 cm. after fixation. The albuginea was intact, somewhat thickened and pinkish white. The mass was solid and firm. On section (fig. 1) it was seen to be composed almost entirely of tumor, with the exception of a small gray-brown, nonpigmented area at the lower pole, which was completely demarcated from the tumor proper by a thin fibrous capsule which fused with the albuginea. This area ostensibly consisted of compressed, atrophic, residual testicular tissue. The tumor had a glistening, cellular appearance. It was dark brown with a greenish cast, with here and there small gray areas. It was irregularly divided by fibrous septums derived from the albuginea. The epididymis and vas deferens were not remarkable.

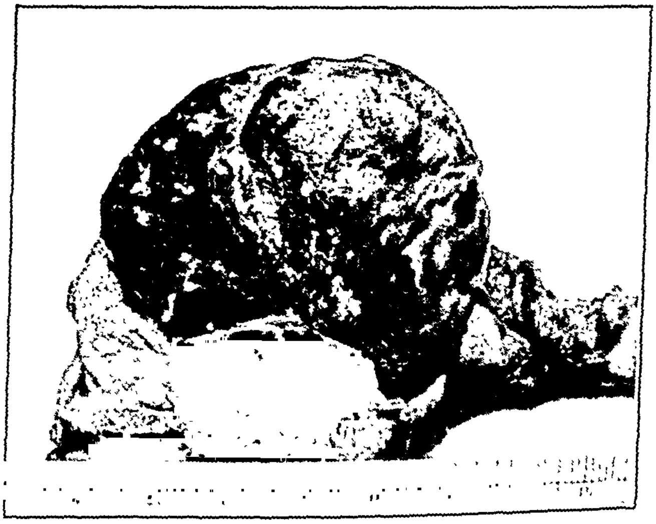

Fig. 1.—Gross view of a cut section of the tumor (long axis oblique). Note the testicular rest—the light area in the lower left hand corner.

Microscopically, the tumor tissue was seen to be composed of anastomosing strands, nests or broad sheets of epithelioid cells. Often the arrangement was alveolar, resembling salivary gland; in other places the resemblance to liver was striking (fig. 2 *A*). The stroma was sparse, consisting of a fine reticular tissue surrounding the pseudo-alveoli and the anastomosing cell cords. Numerous capillaries of one layer of endothelium were present in intimate relation to the cell cords. They were often turgid with blood, and occasionally small extravasations were observed. No necroses were seen.

The individual cells (fig. 2 *B*) were large, though quite variable in size. They averaged about eight to fifteen times the size of a red blood cell, though many were larger. Their state of preservation was good, little or no degeneration being seen. The cells were polymorphous and polyhedral, ovoid, round or irregular. The nuclei were also variable in size and small in proportion to the abundant cytoplasm. Most frequently they were about one to three times the size of a red cell, though many were larger, and occasional giant forms were seen. Rarely, two nuclei were seen in a given cell. They were usually oval or round. The chromatin was sparse, though also variable in intensity. Usually one or none, though occasionally two, nucleoli were present. The nuclear membrane was well defined. No mitoses were seen. The cytoplasm was abundant, acidophilic and finely granular. Most cells contained brown or brown-yellow, fine to coarse pigment granules. The pigmentation was of varying intensity, often obscuring the cytoplasm completely, while in other cases it was evidenced only by a fine brownish stippling. The pigment was a lipochrome, as indicated by negative reactions to iron and melanin and an intensification of staining to a golden brown with sudan IV. Some cells contained in addition to the pigment a small amount of neutral fat in the form of small droplets. No Reincke's crystalloids were seen.

There was no invasion of the albuginea or of the gray-brown nodule, which proved to be compressed parenchymal residue. It consisted of a collection of atrophic, compressed seminiferous tubules, with slightly thickened membrana propria of an intact outer elastic layer and an inner, slightly augmented, collagenous layer. The epithelium was atrophic, showing only one to two layers of seminal cells. The seminal lineage was always incomplete, and no sign of spermatogenesis was seen. Sertoli cells were present. No interstitial cells were present between the tubules. The intertubular stroma consisted of a small amount of fibrous tissue, which centrally was compressed into a thin fibrous layer, forming the capsule which separated the testicular rest from the tumor proper.

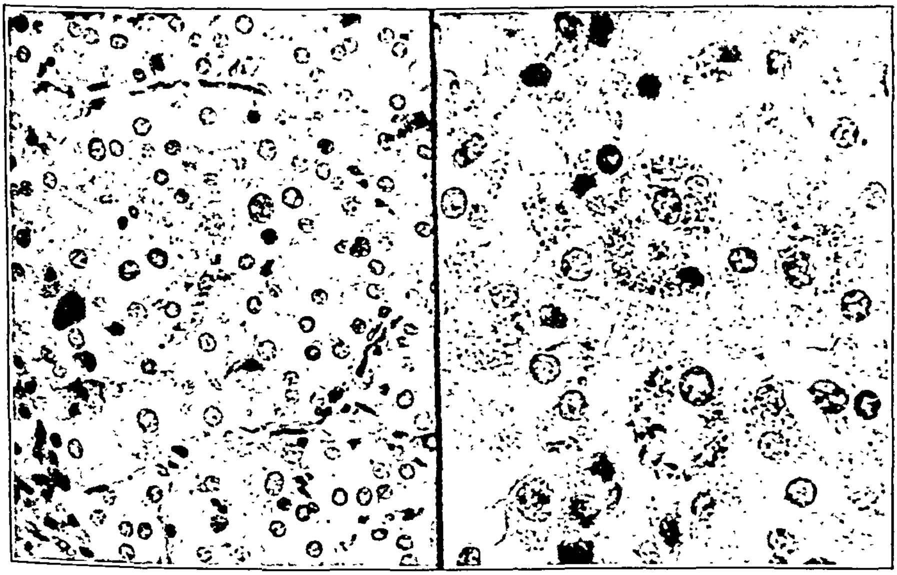

Fig. 2.—*A*, low power photomicrograph of a section of the tumor; hematoxylin and eosin. Note the "liver-like" arrangement, the variability in the size and shape of the cells, the variability in size, shape and staining intensity of the nuclei, the abundant cytoplasm and the capillary encircling a group of cells in intimate relation to them. *B*, high power photomicrograph; hematoxylin and eosin. Note the pigment in the cells.

How completely the cell type observed in this case resembles the interstitial cell is apparent. Both the clinical history and the histologic picture speak for a benign lesion.

COMMENT

It is seen how rare an entity tumors arising from the interstitial cells of the testicle are. Since the existence of tumors of this nature was first suggested by Waldeyer in 1872, only a relatively few reports of tumors of this type have found their way into the literature. In only six of the cases reported can the growth be considered as indubitably arising from the interstitial cells—the case of Chevassu, the two cases of Kaufmann, the case of Masson and Sencert, the case of Panà and the case here presented. The tumor in Dürck's fourth case and in de Jong's case may possibly also belong to this group.

In the last analysis, the etiology of these growths is of course unknown. No feature of apparent etiologic significance was present in the cases of Masson and Sencert and of Panà and in the case reported here. However, certain features were present in the other cases which may possibly have some causal bearing. Kaufmann's patients were brothers. In one, the lesions were bilateral, and in the other, possibly so. A hereditary congenital basis is suggested here. In Chevassu's case the growth occurred in an inguinal testicle in sequence to a previous operation for hernia on that side. Testicular tumors are about one hundred to one hundred and fifty times as frequent in undescended as in descended testes, and the trauma of the operative procedure may have been an additional factor. On the other hand, parenchymal atrophy with secondary hyperplasia of the interstitial cells of varying degree occurs commonly as an accompaniment of ectopic testicular position, and one must therefore keep in mind the possibility that tumor formation may occur on the basis of a previously existing hyperplasia.

Although individual cases may differ in details, the microscopic picture is really sufficiently characteristic to permit the isolation of a special independent form of tumor. In general, there seems to be no preferred age group, the cases reported occurring in persons from 16 to 62 years of age. One growth occurred in an undescended testicle; the other five, in fully descended testicles. The color, depending on the presence or absence of pigment and the amount of fat, was variable. It was reddish yellow in Chevassu's case, grayish in Masson's, brownish red in Kaufmann's, ocher in Panà's and dark brown with a greenish cast in the case reported here. In all instances the gland was enlarged.

Microscopically, the testicular parenchyma was absent entirely or had been reduced to a few atrophic subalbugineal tubules, enveloped in an imperfect fibrous shell which segregated them from the tumor proper and fused peripherally with the albuginea. In my case the residual testicular tissue was limited to a small rest at the lower pole of the mass, which was separated from the tumor by a fibrous capsule which anastomosed with the albuginea. Where no parenchyma remained, the tumor was limited by the albuginea, which it was never observed to have invaded. Proliferation of interstitial cells such as is ordinarily present in cases of diffuse hyperplasia was always absent between the residual tubules.

The tumor masses were broken into lobules by fibrous septums projecting from the albuginea. The tumor tissue consisted of broad anastomosing cords or large sheets of cells of somewhat epithelioid appearance. The cell type and arrangement were often very suggestive of liver, adrenal cortex or an alveolar tumor of the carotid or salivary gland. The stroma was sparse, consisting of reticular tissue and thin-walled capillaries, often in intimate relation to the tumor tissue. Necrosis and hemorrhage were rare.

The constituent cells were large, though they varied in size. They were polymorphous; usually polyhedral forms were present, though round, cubical and irregular forms were common. The cytoplasm was abundant and homogeneous or granular and contained various inclusions. Fat droplets were usually present in varying amount, at times giving a foamy appearance to the cells. Pigment was not constant. Highly refractile granules having the appearance of secretory granules were present in some tumors. Reincke's crystalloids were never observed. This last was expected, since, according to Lubarsch, these bodies are not present in diffuse testicular processes such as tumors.

The nuclei were relatively small and varied in size. Both relatively and absolutely they were smaller than those found in seminomas. They were vesicular, with a sparse chromatin network of varying intensity, and contained one or two nucleoli. Cell division, both amitotic and mitotic, and occasional plurinucleated cells were observed.

The essential features isolating hyperplasia of the interstitial cells of the testicle from other testicular growths are the polymorphism of the cells, their large size, their abundant cytoplasm, containing lipoid and inclusions of various types, the small chromatin-poor nuclei and the liver-like arrangement. These are sufficient to enable differentiation from other testicular tumors with which these growths may be confused, particularly seminomas and heterotopic adrenal tumors. Hyperplasia may be distinguished by the presence of an etiologic factor, by the diminished testicular volume and by the focal intertubular situation of the proliferating cells.

The treatment, as with other testicular tumors, is orchidectomy. This should be followed by postoperative irradiation because of the possibility of malignancy, despite the fact that in only one case (Masson's) was the growth clinically malignant.

SUMMARY

The interstitial cells of the testicle may be the source of hyperplastic or neoplastic lesions. The characteristic cell is of variable size, is polymorphous and contains abundant cytoplasm, with various inclusions, and a relatively small nucleus poor in chromatin.

Hyperplasia occurs secondarily to atrophy of the testicular parenchyma due to some general or local condition. The proliferation is always focal though diffuse, and intertubular, though parenchymal atrophy may have progressed to such a degree as to make the intertubular situation of the proliferation not readily appreciable. The testicle is usually considerably reduced in size.

Neoplasia of the cells of Leydig is an extremely rare condition and is frequently confused with hyperplasia and with seminoma. The characteristic features of this type of growth are the cell type, the enlargement of the testicle, the absence of an etiologic factor for primary parenchymal atrophy and secondary hyperplasia of the interstitial cells, the demarcation of the lesion from the residual testicular tissue, if present, and the absence of proliferation of interstitial cells between the residual tubules. Though usually benign, the growth may be malignant.

Hyperplasia and neoplasia of the interstitial cells of the testicle in animals are briefly reviewed.

A case of interstitial cell tumor of the testicle in a 35 year old man is reported.

ADDENDUM

Since this article was submitted for publication, there have appeared two further references to interstitial cell tumor of the testicle, and one additional case, previously published, has been called to my attention. For completeness, brief comment on these will be made.

Rowlands and Nicholson reported a case of tumor of the left testicle and macrogenitosomia in a 9 year old boy. The involved testicle measured 5 by 4 by 3.5 cm. No testicular tissue was apparent grossly. The tumor was firm, faintly granular, homogeneous and brownish, with small hemorrhages. The only testicular tissue present was some atrophic subalbugineal tubules separated from the tumor tissue by a fibrous capsule. The tumor was composed of irregular bands and nodules of large closely packed cells separated by strands and sheets of noncellular hyaline stroma. The cells varied in size and shape. The cytoplasm was homogeneous and intensely acidophilic, with degeneration (hydropic and vacuolar forms) common. The nuclei were relatively small and deeply stained, with a fine chromatin network and one or more nucleoli. Many cells were binucleated or multinucleated. Fine granular brownish pigment was present in many cells, and stains for fat showed needle-shaped crystals and small rods in the cytoplasm.

The patient was seen two years after orchidectomy, at which time there was no evidence of recurrence or metastasis. No regression in the signs of puberty had occurred.

Rowlands styled this tumor an adenoma of the interstitial cells of the testicle and attributed on the basis of it an association between the interstitial cells and the development of secondary sex characteristics. The cell type cannot be disputed, but in view of the failure of the premature genital and bodily growth to regress and in view of the absence of studies to eliminate the possibility of some lesion elsewhere that might cause the premature development, one cannot conclusively attribute the precociousness to the growth removed.

Stewart, Bell and Roehlke reported a case of testicular tumor and hypergenitalism in a 5 year old boy. This tumor was a nodule, measuring 1.8 by 1 cm., demarcated from the adjacent testicle, which was somewhat enlarged. The other testicle was normal in size. The tumor consisted of cords and sheets of large cells, with spongy cytoplasm and compact nuclei. The testicular parenchyma showed premature development of the seminiferous tubules. There were no cytoplasmic inclusions. On removal of this testicle there occurred some regression in the size of the penis and disappearance of the pubic hair. Clinically, a roentgenogram of the sella turcica showed a normal picture, no calcium was seen in the region of the pineal body and an intravenous pyelogram revealed nothing significant. The authors concluded that the tumor was derived from the interstitial cells and that the excessive genital development was produced by the excessive secretion of the cells composing the tumor.

The cell type found in this tumor is not completely characteristic, lacking the polymorphism of cells and the cytoplasmic inclusions. The illustration in the text, though, shows cells resembling most the interstitial cell. The conclusions, however, as to the relationship of this tumor to the premature development are not warranted. First, the clinical studies do not quite rule out another focus. Second, the premature development of the testicular parenchyma may well have been the causal lesion rather than one arising secondary to the tumor nodule found. Recent studies have resulted in evidence rather against the interstitial cells as a source for androgen, its production being attributed instead to either the Sertoli cells or the germinal epithelium itself.

Budd reported a case of gynecomastia and impotence accompanying a testicular tumor 25 cm. in diameter in a 42 year old man. He said that the tumor microscopically was composed of interstitial cells, but no description of the cells was given. Bell, in discussing the case, stated that the structure of the cells was that of an embryoma of the testis rather than that of an interstitial cell tumor.

One additional case is referred to by Stewart, Bell and Roehlke in their article. This is a case reported by E. Sacchi. A 9 year old boy had the somatic and genital development of an 18 year old youth. There was a tumor of the left testicle measuring 55 cm. in circumference. The tumor is poorly described. According to Sacchi it consisted of masses of cells of an epithelial appearance and alveolar arrangement. The cells had large nuclei and abundant granular cytoplasm. Corpuscles of various sizes were present in the cytoplasm, nuclei and stroma. These, the author thought, were coccidia. He labeled the growth an epithelial tumor with coccidiosis. Orchidectomy was followed by a regression of the beard, the hair on the arms and legs, the deep voice and the erotic tendency that had previously been manifest.

Stewart and his co-workers, in discussion, stated that the pathologic interpretation was incorrect and that the tumor was really an interstitial cell tumor. They arrived at this conclusion largely on the basis of the bodily changes which occurred on removal of the tumor. This, however, seems to be reasoning after a fact which in itself is not established. F. Parkes Weber referred to the same tumor as a carcinoma-like tumor. He further stated that it would be interesting to know whether any testicular tumors in such cases (macrogenitosomia) could justifiably be regarded as endocrine primary tumors of the interstitial cells.

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A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 832)

BLADDER

Carcinoma.—Bumpus and Silver[38] reviewed all cases of tumor of the bladder observed at the Los Angeles County General Hospital between June 1927 and June 1934. The last date was chosen in order that at least two years might elapse after the last treatment and the final results could be accurately evaluated. There were 135 cases in the group. In 36 the carcinoma was so far advanced that no surgical treatment could be employed, and in 8 merely palliative cystotomy was undertaken; all of the patients died in the hospital. The group of 99 remaining cases seems sufficiently large to suggest what is accomplished by the present methods of treatment in large charity hospitals with constantly changing visiting staffs. Eighty-nine per cent of the patients were traced for from three to five years.

Destruction with diathermy was used in 77 of the 99 cases, in 34 through the urethra and in 43 by transvesical exposure. In the former group of cases 17 of the patients were living from three to five years after transurethral electrocoagulation (50 per cent of apparent cures); 11 were known to be dead, and the condition of 5 could not be checked;

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[38] Bumpus, H. C., Jr., and Silver, Barney: Tumors of the Bladder, J. Urol. 37:141-147 (Jan.) 1937.

moreover, 2 of the 11 who were known to be dead lived *more than* five years before they succumbed to recurrences.

The tumors in 25 of the 43 cases in which transvesical treatment was used were of the papillary type; in this group 16 of the patients were known to be dead and 7 had lived more than three years. In 18 of the cases the tumors were of the infiltrating type; in this group 14 of the patients were known to be dead and but 1 was known to be alive more than three years after operation. Fourteen patients (35 per cent) died as a result of the operative procedure. Since at least 8 patients were alive from three to five years after the operation and 30 were known to be dead, there would seem to be approximately a 19 per cent possibility of cure by this method. Improvement of results in the future must evidently come from a reduction in the operative mortality, so that 35 per cent of the patients are not immediately eliminated from all possibility of cure. Some surgeons have felt that the high mortality was largely due to involvement of the ureteral orifices in the destruction produced by the cautery. In 13 of the 34 cases in which the patients were treated transvesically, it was noted that the ureteral orifice had been included in the destruction, but the convalescence was affected in only 1 of the cases. In the series in which transvesical treatment was employed a ureteral orifice was included in the destruction produced by the cautery in 29 cases, and in 10 cases it was considered a decided factor in an unsatisfactory convalescence if not a direct cause of the patient's death. In the series of 29 cases in which the lesion was inoperable, the extensive destruction produced by cauterization involved the ureteral orifice in all the cases in which death occurred, and in several cases the resulting inflammatory process extended along the course of the ureters to the perivesical tissue. Certainly, wherever possible, the insertion of a catheter into an involved ureter and its retention there during the first days of convalescence should be an aid in reducing the high mortality of transvesical thermal destruction. Apparently such destruction is best accomplished by diathermy, for of 8 patients treated with the Percy cautery 4 died immediately after operation, and 2 others were known to have died later.

Kraas[39] described in detail a case of cystadenoma of the bladder. Differential diagnosis of this condition and endometriosis was difficult and could be made only by the pathologist. Endoscopic resection with coagulation of the base of the tumor was successful and effected complete recovery. The symptoms were those of a tumor of the bladder with exacerbation during the menstrual periods.

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[39] Kraas, Ernst: Cystadenom der Blase-endovesicale Exstirpation, *Ztschr. f. urol. Chir. u. Gynäk.* **42**:411-415 (Dec.) 1936.

Chauvin[40] reported a case of tumor of the bladder with an adenomatous structure in a man aged 51. The tumor, which was composed mostly of connective tissue fibers, contained irregularly disseminated glandular acini, lined with a double layer of cuboid and often cylindroid cells; most of the acini were empty, and a few were filled with a homogeneous exudate which had the staining reactions of mucin.

Only 23 cases of vesical adenoma have been reported in the literature. The glandular structure of such tumors is so varied that one may say there is no uniformity of type. It is impossible to deny that they are glandular, notwithstanding Sappey's assertion that the normal mucosa of the bladder contains no glands. Various other authors, however, have examined glands in the wall of the bladder microscopically, and although the histologic structure has been variable, the topography was nearly the same: the glands were strictly localized in the vicinity of the neck of the bladder, from which they may invade the trigon and the anterior aspect of the bladder. Cruveilhier alone maintained that they could be found in any part of the wall of the bladder, and Chauvin's present case, in which the tumor was behind the ureteral orifice, seems to substantiate this claim.

In structure, these tumors may be simple evaginations of the mucosa; they may be of prostatic type, as if representing aberrant lobes of the prostate; some have been found composed of true mucous glands, better differentiated, but always of small size and of acinous or tubular structure; others have been lined with epithelium of intestinal type. It must be admitted that these glands are not found in all persons; they are rare, and the tumors to which they give rise are exceptional. They have been attributed by some authors to irritation or local inflammation. Some of the tumors resemble adenoma of the prostate, some are of tubular appearance and some are cystic adenomas. In short, the tumors are anomalies, and it would be difficult to try to establish any general rule with reference to their formation.

Kutzmann[41] stated that leiomyoma of the bladder, as well as other mesothelial tumors of the bladder, is rare. The leiomyoma is a benign growth of the smooth muscle; its etiology and pathogenesis have been but vaguely explained on the basis of embryonic rests. The usual symptoms may be hematuria, disturbances in micturition and an associated feeling of pressure in the bladder. In some cases there have been individual leading signs or symptoms, as in the case observed by the author in which the tumor protruded through the urethra and caused subsequent subcapsular hemorrhage. Diagnosis can be made by routine urologic procedures. The condition in the female is not to be confused with pelvic disease, and that in the male is not to be confused with benign hypertrophy of the prostate gland. Treatment consists of endovesical procedures or cystotomy with wide resection of the involved wall of the bladder. Prognosis is good, since nearly all leiomyomas of the bladder remain benign. A proved instance of leiomyoma of the bladder is reported.

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[40] Chauvin, E.: Tumeurs vésicales a structure d'adénome, J. d'urol. **42**:521-531 (Dec.) 1936.

[41] Kutzmann, A. A.: Leiomyoma of the Urinary Bladder, J. Urol. **37**:117-132 (Jan.) 1937.

Colston and Leadbetter[42] reported a case of metastasis of carcinoma of the bladder to the brain. The interesting feature in this case was the remarkable response of the extremely malignant primary growth to high voltage roentgen therapy and to radium therapy; although no gross evidence of tumor was present at a careful necropsy, microscopic sections revealed that viable cancer tissue was still present in the deeper portions of the wall of the bladder. Evidence of metastasis to the brain became apparent soon after treatment was completed and rapidly determined the fatal outcome. Studies of the literature have shown the rarity of reports of cerebral metastasis in cases of tumor of the bladder. The similarity of this case to that reported by McKay is striking, in that in both instances there was a remarkable response shown by the original tumor to high voltage roentgen therapy and radium therapy, although in neither instance was the local growth entirely eliminated. Furthermore, metastasis to the brain occurred in both cases and was responsible for the fatal outcome. There was no evidence of metastatic deposits elsewhere in the body.

Rathbun[43] reported 91 cases of carcinoma of the bladder, in 63 of which the condition was proved and complete histologic data were presented. The histologic classification was epidermoid carcinoma in 45 per cent, papillary carcinoma in 29 per cent, adenocarcinoma in 16 per cent and scirrhous, medullary and undetermined types in 10 per cent of the cases. The author's results have been far from encouraging. Fifteen patients were alive and, with one exception, free from any signs or symptoms of recurrence at the end of three years. However, in the next two years 8 of these patients had recurrences and died, which left a five year salvage of only 7 patients (11 per cent).

As to the diversity of published results, these vary from results no better than Rathbun's to as high as 45 per cent of control. Some of the reports are based on a three year cure. This, Rathbun stated, is wrong. He was sure there is a heavy mortality between the three and the five year period. He also stated that considerable confusion exists as to what constitutes carcinoma of the bladder and how the tumor should be graded in relation to the degree of malignancy.

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[42] Colston, J. A. C., and Leadbetter, W. F.: Brain Metastasis in Carcinoma of the Bladder, Tr. Am. A. Genito-Urin. Surgeons 29:261-272 (May) 1936.

[43] Rathbun, N. P.: Comments on Bladder Carcinoma: Classification—Prognosis—Treatment, Tr. Am. A. Genito-Urin. Surgeons 29:255-260 (May) 1936.

He expressed the opinion that when practicable all cancers of the bladder should be radically excised. This would appear a simple position to take if it were not for the fact that because of their usual situation only a small percentage of such carcinomas lend themselves to this type of treatment. The fact that the growth invades one ureteral orifice should be graded in relation to the degree of malignancy.

In the present wave of enthusiasm over transurethral operation there is a decided trend toward the employment of the cystoscopic approach in these cases. This may easily be overdone. This approach should be reserved for very small growths, particularly small recurrent growths. The application of more than four radium seeds through the cystoscope has been rather unsatisfactory. For one reason and another, especially bleeding, it is difficult or impossible to implant them with any degree of accuracy.

As carcinoma remains confined to the bladder, with no disposition to extend by metastasis or otherwise for a considerable period of time, total cystectomy would seem the ideal treatment. The operation per se is not technically difficult, but there are two rather formidable obstacles to overcome. The first is the disposition of the ureters. Ureteral transplantation to the bowel, even in the most skillful hands, carries with it a mortality which is almost prohibitive, transplantation to the groin or bilateral nephrostomy leaves a state of affairs which is far from ideal. This leads one to the second obstacle, which is the selection of cases. The cases in which the condition is very advanced are hardly ideal, in spite of the fact that most total cystectomies are done in this group. Some of the cases in which the condition is not so far advanced might seem to be eminently suited for this operation if it were not for one important item: There is no question but that in some of these cases the condition is entirely and completely controlled by radium, and one certainly hesitates to condemn any human being to total cystectomy with all of its implications if there is even a remote chance of saving the bladder.

Roentgen therapy is still in its infancy. Modern roentgen therapy is a powerful agent and has potentialities for evil as well as for good, as is evidenced by the fact that within the past year one of Rathbun's patients died directly from its effect and another presented alarming symptoms for several weeks. It remains for the future to determine its place in the therapeutic armamentarium.

Graves, Kickham and Nathanson[44] expressed the opinion that the bladder should be considered an integral part of the problem of carcinoma of the uterine cervix because of the great frequency with which it is involved by the disease itself or as a result of treatment. They recommended cystoscopic inspection in the routine examination in all cases before instituting therapy and at intervals thereafter. By this means, when the bladder is found to be normal a base line will be afforded for comparison with later observations as the carcinoma progresses. When, on the other hand, intravesical invasion is found to have taken place, the diagnosis as regards the extent of the disease at once will be rendered more accurate, and information of definite prognostic value also will be obtained. It should be emphasized, however, that extension of the disease into the bladder from the cervix should not be considered a deterrent to vigorous treatment of the malignant process. The authors reported 1 unusual case in which there was extension even to the point of vesicovaginal fistula at the time of the first examination. After treatment there was no evidence of active carcinoma. The fistula remained of course, but that is not too high a price to pay for successful cure.

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[44] Graves, R. C.; Kickham, C. J. E., and Nathanson, I. T.: The Bladder Complications of Carcinoma of the Cervix, Surg., Gynec. & Obst. **63**:785-793 (Dec.) 1936.

Farrell and Fetter[45] studied 72 cases of carcinoma of the bladder; 67 of the patients were males and 5 were females. At the time of the report, 27 of the patients were still alive and under observation, 3 (4.1 per cent) for five years or more and 25 (34.7 per cent) for from one to five years; 45 were dead. In 70 cases the diagnosis was confirmed by histologic examination of tissue. Contrary to experience with carcinoma generally, in a case of carcinoma of the bladder the younger the patient, the better the prognosis. The disease is rapidly fatal, for of the 45 patients who died, 23 (51.06 per cent) were seen within three months of the onset of their first symptoms, and 13 (28.86 per cent) were examined with the cystoscope. The earlier the initial cystoscopy, the better the prognosis. In 32 (45.40 per cent) of the cases the tumor was inoperable and irradiation was the only available treatment. Irradiation relieves symptoms, particularly hematuria. Because of the rapidly fatal termination in most cases of carcinoma of the bladder, more radical operation and larger doses of radiation would appear to be justified.

Stone.—Siddall[46] studied the cases of vesical calculus in the records of the Canton Hospital from the standpoint of etiology.

In Canton, China, and the surrounding countryside, the one endocrine disease that is rather common is a disturbance of the thyroid gland, including simple goiter, hyperthyroidism and toxic goiter, hypothyroidism and adenoma. Thus, there exist in the same localities some cases of thyroid disease and an abundance of cases of urinary lithiasis. Hyperparathyroidism with general decalcification has not been reported from the Canton Hospital. Nephrolithiasis has been associated with hyperparathyroidism. The stones in such cases, however, are renal; so it is not likely that the parathyroid glands are a factor in the production of stones in South China, where the stones are primary vesical calculi and are composed mostly of uric acid and urates.

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[45] Farrell, J. T., Jr., and Fetter, T. R.: Roentgen Irradiation in Carcinoma of the Bladder: A Series of Seventy-Two Cases, J. Urol. **37**:133-140 (Jan.) 1937.

[46] Siddall, A. C.: Primary Vesical Calculus, J. Urol. **37**:268-279 (Feb.) 1937.

There is a tendency today to attach a great deal of importance to vitamin deficiency as a cause of the formation of urinary calculus in man. In South China the findings do not indicate that the people who suffer from vesical calculus also suffer from either vitamin A deficiency or vitamin A and vitamin D deficiency. The Chinese farmer who has a vesical calculus usually takes an abundance of fresh vegetables. More significant, however, is the fact that most of the calculi seen in South China are composed of uric acid, urates and oxalates and form in acid medium, while the calculi formed in the bladder of the rat that is on a diet that is deficient in vitamins A or A and D are mainly composed of calcium phosphates and carbonates. The one disease due to vitamin deficiency that is common in Canton is beriberi.

The possible relation between a high calcium intake and urinary lithiasis has been pointed out previously. With this in mind, a survey was made of the source of the water supply in Canton and the surrounding country. In Canton, where vesical calculus is not so frequent, it was found that the river water, which is used by the poorer classes for cooking and making tea, is low in calcium. On the contrary, in the rural districts, where calculus is common, the household water supply is from wells, and this well water is extremely hard. The elixir of life for the southern Chinese is tea. The long-established habit of drinking tea and the fear of drinking raw water probably grew up from the observation that those who drank raw water were subject to frequent disastrous diseases. The ingestion of caffeine in the tea stimulates the excretion of endogenous uric acid, and a farmer who drinks 1,300 cc. of tea a day consumes from 2 to 4 grains (0.13 to 0.26 Gm.) of caffeine daily, provided all the caffeine is dissolved in the water.

Urinary calculi in inhabitants of South China are vesical and rarely renal. Apparently, the habits of eating, drinking and working in this section supply the fertile soil in which primary vesical stones are easily grown. The urine is concentrated, and uric acid and oxalates are present in relatively large amounts. It is possible that the factor which actually plants the seed or nucleus of the stone is recurrent albuminuria. It has been shown by Nicols and Hoecker that strenuous exercise at times can cause severe albuminuria in a normal subject. If this is true, it is certain that the Chinese farmer who works hard with his hands must have recurrent waves of albuminuria just at the time when the factors are operating to increase the excretion of endogenous uric acid. When the Chinese farmer works the hardest he eats more vegetables, which increases the excretion of oxalate in the urine. It is further suggested that the albuminuria may disturb the protective colloids in the urine and cause precipitation of the uric acid and oxalate. But these constituents must stick together in order to form a nucleus, and time is required. In other words, a certain amount of stagnation of the urine is required, and the most likely place for such stagnation is in the bladder instead of in the kidneys. The farmer of southern China perspires freely, and it may be hours before he voids a small amount of urine. Perhaps many times soft balls of urates and oxalates held loosely together by the albumin are broken and voided, but sooner or later one bit will remain in the bladder an abnormally long time and form the nucleus of a stone.

Bilharziasis.—Giraud and Crosnier [47] reported a case of filariasis and bilharziasis in a Senegalese soldier. The latter infection was observed in three stages, of primary, secondary and tertiary lesions. The presence of filariasis was revealed by the characteristic chyluria without lipuria; the chyluria was of parasitic and not of tumorous origin. In view of the successive findings, it was believed that the chyluria was due solely to the filariasis and that the transitory presence of blood in the urine was due to the bilharzial parasite, while the presence of leukocytes in the urine was due to the combination of the two infections. The fair condition of the patient and the absence of anemia suggested that the bilharziasis had not been present long and that the parasite had been rather recently acquired.

The essential feature in the case was the demonstration of the chyluric syndrome, since the etiology of this condition has not always been so well proved. In the case under consideration Filaria Bancrofti was found not only in the blood, especially at night, but in the urine from the left kidney, while the urine from the right kidney was normal. Roentgenograms made after injection of an opaque substance into the left kidney revealed extracalical images which the authors did not hesitate to interpret as injected intraparenchymatous lymphatic canals. The pyelograms were sufficiently clear to give an idea of the site of the lesions in the left kidney. This unilaterality of the lesions has been pointed out by several authors. Giraud and Crosnier can thus confirm the opinion of those writers who say that chyluria does not always come from the bladder. They upheld the possibility of a mechanical theory for parasitic chyluria, without any necessary pathologic action of the microfilaria. The injected lymphatics were larger than normal; they were the site of true varices, due to obstruction of their lumens, which were caused by the parasites which had found their way into

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47. Giraud, D., and Crosnier, R.: Bilharziose vésicale et filariose urinaire. J. d'urol. **42:**501-510 (Dec.) 1936.

the excretory passages of the kidney, where they produced chyluria. The authors also observed that the opaque substance itself appeared to have some curative action on the infected urinary tract, irrespective of whether a solution of sodium iodide, sodium bromide or silver nitrate was used. This idea was first put forward by the Japanese, Inoue, who attributed the efficacy of the treatment to the irritating effect of the substance injected. He advised continuing the instillation until a slight sensation of pain betrays its entrance into the lymphatic fistula. The authors, without knowing it, realized these conditions in making the pyelograms, and in their opinion this is the reason that the chyluria disappeared after a single instillation of a few cubic centimeters of the sodium salt of diiodomethane sulfonate.

The premature departure of the patient made it impossible to check the permanent results. It is well known that these infections are likely to recur. The mode of action of the injection is not known. The authors suggested that it may serve to obliterate the lymphatic fistula by a reactive edema. Its action seems comparable to that of sclerosing injections into varicose veins.

Cystitis.—Randall and Campbell[48] reported 5 cases of cystitis with alkaline incrustation in females in the absence of an obstructive lesion. The main method of relieving the symptoms of this type of cystitis and of obtaining a permanent cure is acidification of the entire urinary tract, regardless of the causative organism. The variability of the p_H of the urine from separate renal pelves was emphasized. The necessity for acidification of the upper part of the urinary tract, whether or not it is infected, is exemplified by the results of the treatment in the cases reported. Acidification of the urinary tract cannot be obtained by the oral administration of drugs or by acid-producing diets in the presence of cystitis with alkaline incrustation. Supplementary irrigations with acid solutions are necessary to foster an acid atmosphere, which may then be maintained by acid-producing drugs. In their experience, phosphoric acid has been the most satisfactory vesical irrigant to produce an acid medium. A 1 per cent solution is suggested for the bladder and a 2 per cent solution for the renal pelves. The pelves of the kidneys are most tolerant to this solution, but the bladder may at first rebel, in which case weaker acids are used to build up the tolerance of the bladder until solutions of phosphoric acid are accepted.

Dysfunction of the Nervous System.—Creevy[49] stated that a number of diseases of the nervous system may, by lessening the acuity of sensation in the bladder, lead to infrequent micturition, overdistention of the bladder, deficient oxygenation of the detrusor urinae muscle and loss of expulsive force. The development of an obstructive lesion at the vesical outlet will cause urinary retention in such cases when the obstructing force is still slight. The patients may be treated satisfactorily by removal of the obstructing force, provided some sensation remains and the expulsive power of the bladder can first be restored. Expulsive force may be restored in most instances by rest of the detrusor urinae (intermittent or continuous catheterization for mild dysfunction and suprapubic cystostomy for more advanced disorders) and drug therapy (pilocarpine or mecholyl). When this is done, prostatic massage, urethral dilatation and transurethral resection may be employed to relieve the obstruction. Education is important in insuring continued emptying of the bladder postoperatively; this should consist of teaching the patient to micturate at regular intervals, in a leisurely manner, by using the sitting position, manual pressure and a series of voluntary efforts. Atrophy of the detrusor urinae which is so severe as to prevent restoration of contractility, almost complete loss of sensation and mental deterioration will defeat these measures and contraindicate their employment. Nine instances of successful application of these methods and 3 of failure were reported.

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[48] Randall, Alexander, and Campbell, E. W.: Alkaline Incrusted Cystitis, J. Urol. **37**:284-299 (Feb.) 1937.

[49] Creevy, C. D.: The Treatment of Neurogenic Vesical Dysfunction Complicated by Lesions of the Vesical Outlet, J. Urol. **37**:513-517 (April) 1937.

PROSTATE GLAND

Arterial Distribution.—Flocks [50] described the distribution of arteries within the prostate gland in the infant prostate, the normal adult prostate, the prostate showing hyperplasia, the carcinomatous prostate and the prostate after transurethral resection.

There are two groups of arteries within the prostate gland: the capsular group, which show little change with age and with the occurrence of hyperplasia, and the urethral group, which enlarge significantly with age and markedly when hyperplasia is present. The latter group is important in the consideration of transurethral prostatic resection and local repair after this operation, for two reasons: (1) In its anatomic arrangement the urethral group of arteries penetrates at the prostatic vesical junction and then turns distally in a course more or less parallel to the urethral surface, and (2) in its ultimate destination this group of arteries forms the main source of blood supply to the hypertrophied portion of the prostate gland.

Genesis of Hypertrophy.—In conformity with the studies of Reischauer and Grassmann, Pollak [51] found multiple parenchymatous foci in the periurethral prostatic tissue in many cases of early prostatic hypertrophy. These foci may later become fibromuscular nodules. At the same time numerous nodules are forming in the periurethral glands. In practically all cases of advanced prostatic hypertrophy a growth of the epithelial and mesenchymal parts of the organ is found. Everything points to the fact that hypertrophy is a change which occurs in every old prostate gland but causes clinical symptoms in only a few. Prostatic hypertrophy is caused by a decrease in the formation of androgen, setting free heterosexual influences which had been restrained up to that moment. The term "prostatic hypertrophy" best describes the changes found and should not be altered for another more modern term.

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[50] Flocks, R. H.: The Arterial Distribution Within the Prostate Gland: Its Rôle in Transurethral Prostatic Resection, J. Urol. **37**:524-548 (April) 1937.

[51] Pollak, Walther: Zur Genese der Prostatahypertrophie, Ztschr. f. Urol. **31**:49-67 (Feb.) 1937.

Resection.—In order to obtain data for a report which covered 27,000 transurethral prostatic resections, Chetwood [52] sent questionnaires to 800 members of the American Urological Association.

Nine hundred and eighty-six deaths were reported; no cause was given for 822, but the causes were probably divided between hemorrhage and infection, which constituted the largest number of causes reported. Other causes named were perforation of the bladder, rupture of the bladder, embolism, pyonephrosis and explosion during operation.

The most common complications reported by 98 per cent of the operators (none reported by 2 per cent) were hemorrhage, varying from that of a controllable degree to that requiring suprapubic cystotomy, and infection, local and general, varying from mild pyuria to perivesical cellulitis and gangrene and occasionally septicemia. Other complications enumerated were urinary extravasation, pyelitis, pyelonephritis, uremia, thrombosis, chronic urethral cystitis, stricture, incontinence and epididymitis.

Respecting the percentage of cases in which transurethral prostatic resection is adaptable: Chetwood found that it was variously claimed to be from 75 to 98 per cent and even 100 per cent. Seventy-five per cent would be a notable achievement, 98 per cent would be doubtful, and if it was 100 per cent the operation would be a panacea, which it is not.

Emmett,[53] in discussing relief of postprostatectomy vesical dysfunction, stated that two main classes of patients are recognized: those who have never been relieved by prostatectomy and who seek relief within three years after the operation and those who have experienced complete relief for many years but who finally suffer from a recurrence of obstruction, either with recurrence of benign hyperplasia or with the formation of carcinoma after the original operation had been performed for benign hyperplasia. The latter group demonstrates the fact that prostatic hyperplasia does recur and also that total prostatectomy is no insurance against the formation of prostatic carcinoma.

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[52] Chetwood, C. H.: Summary of Over Twenty-Seven Thousand Cases of Transurethral Prostatic Resections, Tr. Am. A. Genito-Urin. Surgeons **29**:213-217 (May) 1936.

[53] Emmett, J. L.: Relief of Post-Prostatectomy Vesical Dysfuction by Transurethral Surgery, J. Urol. **37**:569-581 (April) 1937.

Sixty-seven cases were reported in which transurethral prostatic resection was necessary subsequent to prostatectomy in order to control symptoms. Forty-two of the patients underwent resection three years after prostatectomy, and half of them, in addition to having marked symptoms of obstruction, were suffering from a persistent suprapubic sinus.

The three most common types of obstruction found were obstruction due to a cicatricial, deformed prostatic urethra and neck of the bladder, that due to remaining prostatic tissue and that due to carcinoma. An extremely high percentage of patients may be relieved of their symptoms by transurethral prostatic resection.

Bumpus and Massey[54] reviewed 71 cases from private practice in which prostatic obstruction was treated by transurethral resection; in 80 per cent of the cases there was no preliminary preparation. Thirty-eight per cent of the patients were more than 70 years of age. The average period of hospitalization was less than one week. There was 1 death. This same trend in the abandonment of preliminary treatment in resection is borne out at the Mayo Clinic, where during 1935, 765 resections were done with but 7 deaths; 65.7 per cent of the patients received no form of preliminary drainage.

In the series of cases at the Mayo Clinic but 3.9 per cent of the patients received suprapubic drainage prior to resection during 1935. Alcock had used it in only 30 of his 1,400 resections, an incidence of 2.1 per cent, while Bumpus and Massey had employed it in 16 per cent of their resections. Thirteen patients, or 18.1 per cent, were subjected to suprapubic cystostomy. The average age of these patients was 71 years. An average of 26.8 Gm. of tissue was removed, and the total time spent in the hospital for cystostomy and resections averaged twelve and a half days per patient.

Negley[55] submitted two tables containing data on patients from Los Angeles and vicinity. In these tables he contrasted the surgical procedures, preoperative preparation, complications, stay in the hospital and mortality in cases in which prostatectomy was performed with those in which resection was performed. He listed charity patients in table 1 and private patients in table 2.

Table 1, which is a résumé of the work of approximately 30 urologists, would seem to show that all of them still prefer some sort of preliminary drainage in all cases in which prostatectomy is performed and in 78 per cent of those in which resection is done. There was a difference of only five days in the preoperative preparation in favor of resection. Prostatitis was a complicating factor in only 50 per cent of cases. Complete retention in almost five times as many cases in which prostatectomy was performed as in those in which resection was done would seem to compel more pretentious preparation in the former. Another reason why a patient who is to undergo resection needs less preparation is that in many cases resection is done for relief of symptoms rather than because of large amounts of residual urine. Deaths following resection outnumbered those following prostatectomy in the proportion of 2 to 1, but most of the deaths from resection were the result of surgical accidents.

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[54] Bumpus, H. C., Jr., and Massey, B. D.: Transurethral Resection: Does It Require as Exacting a Preoperative Preparation as Prostatectomy? California & West. Med. **46**:89-91 (Feb.) 1937.

[55] Negley, J. C., in discussion on Bumpus and Massey,[54] p. 92.

Table 2 presents a résumé of the records from a large private hospital; it represents the work of general surgeons as well as urologists and would seem to show that there is a difference of only eight days in the preoperative preparation in favor of resection. Again the untoward results of an indwelling catheter were present in only 8 per cent of cases in which combined methods were used. The fact that complete retention was more frequent (2:1) in cases in which prostatectomy was performed would seem to necessitate longer preparation in such cases. Deaths from resection outnumbered those from prostatectomy 6 to 1; 75 per cent of them were due to pyelonephritis and uremia. The most important factor bearing on preoperative preparation is that 73 per cent of the patients who had resection entered the hospital only one day prior to operation; 75 per cent of the deaths occurred in this group. Surely, this shows that preoperative preparation might have helped.

In conclusion, Negley stated that any group of patients 65 years or more of age, many of whom have myocardial disease, renal disease, prostatitis and infected urine, cannot be standardized but must be treated individually, both as to preparation for operation and as to the type of operation. Certainly, one who has reached the "prostatic age" is entitled to a rest in bed for a week or more before operation is done, as a reward, if for nothing else.

Blatt[56] discussed the cases of obstruction of the neck of the bladder observed at the Rubritius Clinic during the last fifteen years. He accepted Marion's classification, which divides the diseases of the neck of the bladder into three groups: contracture of the neck, hypertrophy of the sphincter and glandular hypertrophy of the neck. Blatt stated

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56. Blatt, Paul: Die Sphincterkeilexcision bei den Erkrankungen des Blasenhalses (Sphincterhypertonien und Spinctersclerosen), Ztschr. f. urol. Chir. u. Gynäk. **42**:31-47 (Dec.) 1936.

that the third group consists of small adenomas of the prostate, which are often difficult to see, even during operation. This condition was formerly called atrophy of the prostate. The author observed 15 cases of hypertrophy of the sphincter; the patients were all treated by cuneiform excision of the sphincter through a suprapubic incision, with good success. There were 13 cases of contracture of the neck of the bladder; the patients were treated by cuneiform excision. The results were successful in 12 cases, but 1 patient died of ascending infection of the kidneys.

Postoperative Mortality.—Rolnick and Riskind[57] reviewed the records of the Cook County Hospital for the past five years. The review included a series of 897 cases in which the following operations were performed: cystotomy, cystotomy and suprapubic prostatectomy, perineal prostatectomy, cystotomy and resection and transurethral resection. They were impressed by the fact that there has been a noticeable lowering of mortality among their patients. Previous to the era of resection, two stage prostatectomy had been the routine procedure. With the advent of resection, they were impressed with its value but learned soon that it would not be wise to adopt resection as a routine operation, as had previously been the case with two stage suprapubic prostatectomy. Within the last two or three years the patients have been selected as to their suitability for suprapubic, perineal or transurethral attack, and as a result there has been a lower mortality. The statistics from the Cook County Hospital for 1935 show that of 237 patients operated on, 50 (21 per cent) died. This includes those subjected to all types of operation, including cystotomy. Resection was performed in 110 cases, with 16 deaths (14.5 per cent). In 25 cases in which two stage suprapubic prostatectomy was performed 6 (24 per cent) of the patients died, and in 36 cases in which perineal prostatectomy was performed 4 (11 per cent) of the patients died. It can thus be readily seen that resection has been the largest factor in lowering mortality in some cases in which the patients are poor risks.

Rolnick and Riskind concluded that careful selection of cases and the use of all the routes for attack on the prostate glands have been factors in lowering the mortality. If intolerance to the catheter or marked infection is present, a preliminary cystotomy should be done. Cystotomy, done carefully and under local anesthesia, carries with it practically no mortality. Two stage suprapubic prostatectomy is a satisfactory procedure and carries with it a low mortality in those cases in which the patients can be considered only fair risks. Transurethral resection is the safest procedure for the patient who is a poor

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57. Rolnick, H. C., and Riskind, L. A.: Mortality in Prostatic Surgery, J. Urol. **37**:12-17 (Jan.) 1937.

risk and who does not have a large prostate. Cystotomy followed by resection has little or no mortality and is the safest of all procedures for attack on the prostate gland. A patient who is a good risk for a one stage operation or in whom carcinoma is suspected should be subjected to perineal prostatectomy. The high incidence of occult carcinoma of the prostate gland should be considered seriously in determining the type of operation.

Carcinoma.—In 1935 Bugbee[58] reviewed cases of carcinoma of the prostate which he had observed over a period of twenty-five years. He concluded that in dealing with carcinoma of the prostate gland one is dealing with an essentially fatal disease and that occasional enthusiastic reports of results obtained in isolated series of cases are either immediate results obtained by a certain method of treatment or they represent results obtained in a group of cases in which the patients would react favorably to any method of procedure; the patients have the type of carcinoma, in fact, that would probably grow slowly were no specific treatment employed.

Since 1932 Bugbee has performed 63 resections on 52 patients; there was no operative mortality, but 12 patients died later. Forty patients were alive and had had satisfactory vesical function when last heard from, which was from one month to four years after resection. No radium was employed in any of these cases, and high voltage roentgen therapy was employed only in an attempt to control hemorrhage before operation. In no case did the growth recede under roentgen therapy, and in 2 cases the urinary symptoms were aggravated.

In every case of carcinoma of the prostate with retention observed during a four year period, whether metastasis was present or not, resection had been carried out and urinary function restored. In every case it was possible to pass the resectoscope after sufficient dilation of the urethra. With the orifice well freed of the encroaching growth, it had remained open, certainly for an appreciable length of time; up to the time this paper was written only 3 patients had required reoperation—1 for severe hemorrhage, which was controlled by another resection, and the other 2 for a marked increase in the size of the remaining growth. Nine of the first patients who were subjected to resection required a second resection before they left the hospital. The amount of tissue removed varied from 4 to 56 Gm.

There seems to be less shock associated with resection for carcinoma than with resection for hypertrophy. With the reestablishment of vesical function and the ability of the patient to empty the bladder, tenesmus, dysuria, local congestion and infection subside. If pain has been present in the perineum and legs, this usually diminishes. In 6 instances, a tumor of the bladder, either adjacent to or independent of the carcinoma of the prostate, was removed by resection at the same time as the prostatic resection. In no instance did the growth appear to be stimulated by the resection or was local or metastatic extension accelerated, as has been suggested by some writers.

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[58] Bugbee, H. G.: Experiences with Transurethral Resection in Carcinoma of the Prostate, Tr. Am. A. Genito-Urin. Surgeons **29**:207-212 (May) 1936.

In comparing the results to be obtained with open operation, resection or irradiation, one must realize that circumscribed growths, which often grow slowly, may respond favorably to any form of treatment or do well for a considerable time when left alone, while resection and often irradiation are employed for all types of carcinoma associated with retention, most often for growth in the advanced stage, which would not be considered as suitable for a radical prostatectomy.

Hager and Hoffmann[59] summarized the findings in 396 cases of malignant conditions of the prostate observed at the Los Angeles General Hospital in thirteen years. There were 240 deaths in the series, 186 of which occurred within the first year. Fifty-four patients lived from one to ten years, but few survived for three years. Sixty were reported as living. The authors were unable to trace 89 of the patients.

The scope of treatment in general has been conservative, with the institution of those measures necessary for the relief of urinary obstruction. The subject of metastasis is paramount in the choice and limitation of treatment and also in prognosis. It is probably the deciding factor in the determination of relative cures. Metastasis was demonstrated by roentgenograms at the initial examination in 107 cases and after the first examination in 26 instances, in a period of five years. It is apparent that in fully 25 per cent of cases there was demonstrable metastasis to bone at the time the diagnosis was first made.

Graves, Warren and Harris[60] studied 7 cases of carcinoma of the prostate and 1 case of carcinoma of the bladder by the use of large sections made through the soft tissues and adjacent bones of the pelvis. Perineural lymphatic involvement was a constant feature in the cases of carcinoma of the prostate, but was absent in the case of carcinoma of the bladder. Owing to the abundant nerve supply in and about the prostate gland, opportunity for perineural lymphatic involvement is great. The pain associated with prostatic cancer is clinical evidence of the existence of perineural involvement. While hematogenous metastasis may occur in carcinoma of the prostate, the chief factors in the marked preponderance of metastatic lesions in the pelvis and in the lower portion of the spinal column are the distribution of the nerves and the conduction of tumor along the perineural lymphatics into close contact with the bone. Many metastases occur as a direct invasion of the marrow spaces through the cortical ostia. Early metastases may be missed in roentgenographic study. Conversely, under rare conditions metastases may be erroneously diagnosed, and there actually may be only an irregularity in the extent of resorption of bone. Invasion of the lymphatic channels is a frequent occurrence, and metastases through the usual lymphatic route is an important method in which the disease spreads, although probably this is not a factor in determining the localization of the bony metastases. The perineural lymphatic dissemination of the tumor may be either by continuity or by embolism. Involvement of soft parts, particularly the rectum, seminal vesicles, vas deferens and ureters, can be readily studied by this method.

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[59] Hager, B. H., and Hoffmann, E. F.: Statistical Data on Three Hundred and Ninety-Six Cases of Carcinoma of the Prostate, J. Urol. **37:**180-185 (Jan.) 1937.

[60] Graves, R. C.; Warren, Shields, and Harris, P. N.: Osseous Metastases of Carcinoma of the Prostate with Special Reference to the Perineural Lymphatics, Tr. Am. A. Genito-Urin. Surgeons **29:**179-205 (May) 1936.

Nitch[61] stated that the results of radical operations for carcinoma of the prostate gland have been so disappointing in other than Young's hands that he confines his treatment to conservative or palliative measures consisting of high voltage roentgen therapy, radium therapy, suprapubic drainage, transplantation of the ureters, electroresection or a combination of any of these, as indicated.

As far as high voltage roentgen therapy is concerned, the immediate results are sometimes remarkable, but the ultimate results are disappointing. Some of the severe reactions, such as cystitis, ulcerative proctitis and lymphedema, can be obviated by the split dose method of Levitt, but the best that can be hoped for is a remission of the symptoms for an average of one and a half years.

Nitch used radium in massive doses. Six or eight platinum needles, each of which contains 1 mg. of radium, are placed in the prostate gland through a Young perineal incision. Two needles, each of which contains 3 mg. of radium, are placed in the connective tissue on each side of the prostate gland. The bladder is opened, and a metal box containing 50 mg. of radium is placed on the vesical surface of the prostate. Five milligrams of radium is then placed in the posterior urethra, in a rubber tube attached to a Pilcher bag which surrounds the metal box. The box and the urethral tube are removed in twenty-four hours, and the platinum needles are removed in ten days. Nitch stated that the results of the treatments have been encouraging but by no means startling.

Of the surgical measures, transurethral electroresection is the best for relief of obstruction if the caliber of the posterior urethra permits

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[61] Nitch, C. A. R.: The Conservative Treatment of Carcinoma of the Prostate, Brit. J. Urol. 8:329-336 (Dec.) 1936.

its use. It is contraindicated in the presence of a rapidly growing carcinoma, as relief is of such short duration that suprapubic drainage is a better procedure. Nitch has employed transplantation of the ureters to the intestine in 2 cases but stated that it can be performed only in carefully selected cases. He concluded that in the future electroresection followed by some form of radiotherapy will be the method of choice.

Young[62] reported that recent statistics showed that carcinoma of the prostate occurs in at least 14 per cent of men past 44 years of age. Carcinoma of the prostate is three times as common as that of any other internal organ. In half of the cases this lesion is associated with prostatic hypertrophy. The two lesions are distinct in their origin. In a large percentage of the cases, carcinoma begins in the posterior lobe of the prostate gland, where it is easily palpable by rectum. An area of marked induration should arouse suspicion. A positive diagnosis can be made without danger, by exposure of the growth through the perineum.

If the cancerous nodule is small, it may be radically removed by hemiprostatovesiculectomy. If the growth is more extensive, Young's radical operation has been shown to result in a complete cure in more than 50 per cent of the patients operated on. Many early carcinomas of the prostate gland would be discovered if rectal examination were made during physical examinations on men past 40 years of age. Young stated that the radical operation for carcinoma of the prostate is not difficult and that the mortality is low. Normal micturition and complete urinary control have been obtained in many cases. In those cases in which the patients were not cured but died later of metastasis, the local result was often satisfactory. Young was of the opinion that the perineal route affords the only adequate approach for confirmation of the diagnosis of carcinoma of the prostate and its radical cure. In the presence of benign growths it gives the best results and the mortality is as low as for any other procedure if the patient is observed for a month after operation.

Tuberculosis.—Moore[63] found tuberculosis of the prostate in 20 (12.3 per cent) of 163 cases of tuberculosis. The gross appearance is that of an irregular yellow or grayish yellow homogeneous or finely granular, rubbery or crumbly focus in the peripheral parts of the posterior and lateral lobes. It should be distinguished from carcinoma and dilated acini filled with lipoid-rich inspissated secretion. The lesions are typically caseous. It seems most probable that the bacilli in most cases reach the prostate gland through the blood stream and first invade the periacinal tissue and acinal lumens. There is histologic or correlative evidence that the prostatic lesion is secondary to other urogenital tuberculosis in less than 20 per cent of the cases.

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[62] Young, H. H.: The Radical Cure of Cancer of the *Prostate*, Surg., Gynec. & Obst. **64**:472-484 (Feb.) 1937.

[63] Moore, R. A.: Tuberculosis of the Prostate Gland, *J. Urol.* **37**:372-394 (March) 1937.

URETHRA

Anatomy.—From a comparison of the urethras and necks of the bladders from 30 women with those from 17 girls 4 years of age and younger, MacKenzie and Beck[64] concluded:

> 1. Chronic inflammation of the urethra and bladder neck is present in a higher percentage of adults than we have heretofore imagined.
> 2. Perimucosal structures about the bladder neck and posterior third of the urethra are acquired.
> 3. These acquired structures simulate prostatic tissue because they take origin from the same type of embryologic tissue, and thus have the same inherent properties.
> 4. The stimulus required for the acquisition of these structures may be: (*a*) infection within the genito-urinary tract, (*b*) structural anomalies within the genito-urinary tract or (*c*) trauma of childbirth.
> 5. These buds and nests known as von Brunn cell nests or buds, in so far as they are a proliferation of the mucosal epithelium, develop their lumen from the intra-epithelial glands as seen in the mucosal epithelium in children.
> 6. Those structures about the bladder neck and posterior urethra referred to by previous workers as prostatic structures, we consider to result from a process similar to cystic disease of the upper genito-urinary tract, better known as pyelitis cystica, ureteritis cystica, and cystitis cystica, according to location. We propose to call it cystitis cystica about the bladder neck, and urethritis cystica when it occurs in the urethra.

Tumor.—Dózsa[65] discussed the primary tumors of the female urethra. Of the benign tumors, the most frequent are caruncles, which histologically can be divided into three groups: granuloma, papillary angioma and telangiectasia. Fibroma, fibromyoma and myoma are rare. The common malignant tumor of the urethra is the carcinoma. Sarcoma is rare, and its histologic structure varies greatly. The symptoms of urethral tumor depend on the nature, the size, the position and other peculiarities of the growth. Often symptoms of trigonitis, cystitis and urinary infection complicate the clinical picture. The diagnosis is usually easy to make. Biopsy and urethroscopy are sometimes required. Differential diagnosis has to include rodent ulcer, primary sclerosis and tuberculous ulcer. Treatment of a benign tumor is simple and consists of excision or coagulation; the prognosis is good. Prognosis of the malignant tumor is bad; treatment can effect a lasting cure only when the growth is in the early stage. A carcinoma usually responds well to radium treatment but not so well to roentgen therapy. Most urologists prefer to combine irradiation with surgical removal. The urinary stream must usually be deviated before extensive surgical removal of the tumor is performed, either by suprapubic drainage or by transplantation of the ureters into the bowel. Some surgeons, among them Marion, use a plastic procedure to form a new urethra after resection and close the suprapubic fistula.

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[64] MacKenzie, D. W., and Beck, Sidney: A Histopathologic Study of the Female Bladder Neck and Urethra, Tr. Am. A. Genito-Urin. Surgeons **29**:227-253 (May) 1936.

[65] Dózsa, Eugen: Ueber die Neubildungen der weiblichen Harnröhre, Ztschr. f. urol. Chir. u. Gynäk. **42**:381-395 (Dec.) 1936.

Trauma.—Beach[66] offered the following generalizations regarding the management of the so-called "straddle" injury, based on his experience with 16 cases: Every patient who has a rupture of the urethra, whether partial or complete, should be hospitalized. This is particularly so in cases in which the patient voids spontaneously after the accident; such injuries are the most difficult to handle, and complications develop readily. Many partial ruptures, when catheterization is possible, respond satisfactorily, and no complications develop when an indwelling catheter is used. If catheterization is impossible, operation must be undertaken immediately. The most satisfactory results are obtained by surgical treatment, which should be bold, direct and as simple as possible. Operation must not be too extensive at any one time. It is better only to drain the bladder at first. After a few days of rest, subsequent operation may be carried out with comparative ease.

Simpson-Smith[67] reported 8 cases of rupture of the urethra, each of which furnished some separate point for discussion or improvement in management. In addition, he reviewed all the available cases which had been reported in the past twenty years (approximately 381 cases), in order to present a reliable picture and to measure the trend of modern urologic views.

The site of the rupture was as follows: the bulbous portion of the urethra in 50 per cent, the membranous portion in 40 per cent and the pendulous portion in 5 per cent of the cases and the female urethra in 2 per cent of the cases. In 3 per cent of the cases the site of rupture was not stated. Forty-six per cent of the ruptures were caused by falls, usually with the patient astride some object; 5 per cent were caused by blows, and 3 per cent followed instrumentation of the urethra.

The type of urethral rupture depends on the degree of injury. In partial ruptures either the mucous membrane alone is torn, as in penile injuries, or, more commonly, part of the urethral wall may be split. In complete ruptures a blow sufficient to sever the tough urethra usually causes much crushing of the ends, and the gap thus formed is further increased by the retraction of the elastic tissue. "Complete fracture" of the urethra arises as a result of severe perineal laceration by a blunt instrument.

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[66] Beach, E. W.: The So-Called "Straddle" Injury: Its Management, California & West. Med. **46**:234-239 (April) 1937.

[67] Simpson-Smith, A.: Traumatic Rupture of the Urethra: Eight Personal Cases, with a Review of Three Hundred and Eighty-One Recorded Ruptures, Brit. J. Surg. **24**:309-332 (Oct.) 1936.

The symptoms of traumatic rupture are few and straightforward: they readily lead to a correct diagnosis. Shock, pain, bleeding from the penis, perineal hematoma and ecchymosis, abnormality of micturition and occasional extravasation are the principal symptoms. Shock is severe, even when the extreme end of the penis alone is injured.

The passage of a catheter is the most unreliable means of diagnosis and should not be employed. There are no less than 42 cited instances in which diagnostic catheterization was unsuccessful. In only 6 cases was this procedure definitely forbidden.

A general analysis of the treatment employed disclosed that the perineum was incised in no less than 248 cases, and the bladder was opened in only 181. In only a few of these 181 cases was the bladder definitely recorded as closed at the end of the operation, and so 181 represents the maximum of urinary deviation, that is, just less than 50 per cent. The indwelling catheter was used 180 times. In 105 cases it was employed as a splint to insure the patency of the urethra, for a temporary suprapubic tube drew off the urine; in the remaining 75 cases the catheter alone served the dual purpose of splint and drain. Perineal section was done in 248 cases, and end to end anastomosis was performed in 141 cases. An indwelling urethral catheter was used in 180 cases; the membranous portion of the urethra was injured in 92 of these, the bulbous portion in 83, the penile portion in 2 and the female urethra in 3. Drainage of the perineal wound was employed in 41 cases, and suprapubic drainage of urine was used in 181 cases. The urethral ends were stitched to perineal skin in 16 cases.

In all cases success will depend on the following factors: admission of the patient to a hospital as soon as possible after the accident has occurred and before micturition has been allowed; a careful toilet of any proposed operative site, particularly of the perineum, penis and anterior portion of the urethra; prompt diversion of the urinary stream by a suprapubic incision, if necessary, with use of a local anesthetic; retrogression of a "boiled" gum elastic catheter down the urethra to establish a diagnosis of partial or complete rupture, and discarding of this catheter, if it can be passed, from the meatal rather than the vesical end; wrapping of the penis in a sterile dressing which cannot fall off, to prevent ascending infection during the healing stage, and high elevation of the foot of the bed (allowing several pillows under the head for comfort), to insure that the urine will flow away from the meatus into the fundus of the bladder.

Treatment is urged as soon as possible after the accident and is directed against fouling of the raw area by urine, haphazard catheterization or perineal contamination. Suprapubic deviation is submitted as essential in the treatment of all ruptures, partial or complete. The only exception to this rule is the rare injury to the penile shaft. An indwelling catheter is said to be well tolerated in cases of rupture of the posterior or "membranous" portion of the urethra, and in only a few cases does it produce strictures or necessitate perineal exploration. Rupture of the bulbar portion is certainly prone to the formation of stricture. In the presence of such a lesion suprapubic cystotomy is instantly performed, but an external urethrotomy is postponed until the bruised tissue has recovered, until the necrotic tissue is well differentiated and until accurate end to end suture approximation has a better chance of "holding" and healing. A penile injury is of less serious moment and may not require a suprapubic operation. Injury of the female urethra requires immediate diversion of the urinary stream.

Urethral Glands.—Cabot and Shoemaker[68] discussed the rôle of glands of the female urethra in the production of infection of the urinary tract. This study of a fair amount of material seems to warrant the following deductions:

There is no evidence of true glands in the proximal two thirds of the female urethra. Two specimens were found to contain areas of secretory epithelium in the mucous membrane, but this did not extend into the submucosa. The structures referred to as corpora amylacea by Renner are not specific products of the prostate gland. To refer to them as evidence of glandular structures homologous to the prostate gland simply confuses the issue. The colloid-containing cysts in the urethral mucosa and submucosa are formed from von Brunn's cell nests. The mechanism of their formation is the same as that of the colloid-containing cysts elsewhere in the urinary tract. They may properly be designated as urethritis cystica.

Returning to the question suggested by the title of their paper, namely, the relation of the glandular structures to infection of the urinary tract in the female, Cabot and Shoemaker disagreed with the position taken by Renner, Folsom and others. Their view that glandular structures are the basis of infection does not seem tenable. Their position is further weakened by the well known behavior of the urethra when infected by the gonococcus. This type of infection commonly runs a mild course and goes on to recovery, except when it is complicated by involvement of Skene's or of Bartholin's glands. These glands are generally accepted as homologous respectively to the prostatic glands and the glands of Cowper. But Skene's glands lie in the distal third of the urethra and are out of the field of the present discussion. The glands of Bartholin obviously do not enter at all. Now if there were important glandular masses in the proximal two thirds of the urethra, they would certainly become involved and prolong the inflammatory process. Experience suggests that this does not occur.

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[68] Cabot, Hugh, and Shoemaker, Rosemary: The Rôle of Glands of the Female Urethra in the Production of Infection of the Urinary Tract, Tr. Am. A. Genito-Urin. Surgeons **29**:461-472 (May) 1936.

Looked at from another point of view, inflammation of the urinary tract of the so-called ascending type is notoriously common among female children. These infections are assumed to reach the bladder through the urethra and might properly be expected to invade glandular masses in the proximal portion of the urethra if such existed. As far as is known, chronic posterior urethritis in children is not believed to be a common lesion. Finally, it is notorious that the lesions of the female urethra, to which reference was made at the beginning of this paper, are characterized by normal or substantially normal urine. This speaks against a glandular origin, not for it.

SEMINAL VESICLES

Tuberculosis.—Chauvin[69] stated that the diagnosis of primary tuberculosis of the seminal vesicles may present itself under two variable aspects. The signs may, on the one hand, consist more or less clearly of a refractory urethral discharge, chronic from the start, with moderate pollakiuria or terminal hematuria, which will point toward a lesion of the urogenital level, urethral, prostatic or vesicular, as the case may be. Or, on the other hand, the patient may have no genital symptoms but distinct urinary symptoms which suggest that he is suffering from renal tuberculosis. In this case pollakiuria and slight terminal hematuria, accompanied with pyuria and albuminuria, will in part point toward vesicorenal lesions. In cases in which the urine contains pus, albumin and Koch bacilli, the nature of the lesion is easy to determine; it is its localization that is difficult. Negative findings when the ureters are catheterized and negative results of inoculation will demonstrate that the kidneys are not the site of infection. As it is generally agreed that there is no such thing as primary tuberculosis of the bladder, there are left only the prostate gland and the seminal vesicles as the source of the pus and bacilli. Rectal examination and massage of the prostate gland and seminal vesicles will reveal the state of these organs and assist in diagnosis. But one should still be cautious in making a diagnosis of primary tuberculous vesiculitis and remember that there are renal lesions which remain silent for a long time and which only prolonged observation can exclude.

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[69] Chauvin, E.: La tuberculose primitive des vésicules séminales. Arch. d. mal. d. reins **10**:63 (Jan.); 129 (March) 1936.

In prognosis, when the foci in the seminal vesicles break their bounds, it is usually to the prostate that the tuberculous process extends in an attempt to find its way out into the urethra through a softened prostatic focus. Primary vesiculitis constitutes an initial stage of tuberculous invasion of the urogenital apparatus. All its gravity lies in its possibilities of generalization. Chauvin has never seen renal tuberculosis occur secondary to tuberculosis of the seminal vesicles, but a downward extension from these organs into the genital tract is frequent. Experience has proved that tuberculous lesions of the seminal vesicles occasionally may pass into encystment and disappear, ending in complete cure.

It is agreed that no localized tuberculous process can be cured unless appropriate medical treatment is directed to the modification of the general condition. Such types of treatment as physical therapy, hyperpyrexia and ultraviolet therapy have all been used with some success.

Local treatment must be given with great caution. Massage is liable to spread the infection toward the testes and to cause general septicemia.

Surgical extirpation of the tuberculous lesion, while it seems at first glance to constitute an ideal method of treatment, has not, to Chauvin's knowledge, been carried out, unless exceptionally. He pointed out that vesiculectomy is not so radical an operation as it appears; fine prostatic granules may be left behind unperceived, as may beginning lesions and funiculitis and of the vas deferens. He regarded vesiculectomy as a difficult and grave operation, regardless of the route chosen. He stated that in an immense majority of cases the surgeons who have attempted it have had to be content with atypical and partial resections, always incomplete, or sometimes with simple curettage. Even if these operations may give satisfactory results in the treatment of inflammatory lesions, which are opened and drained widely, they should not be used for a tuberculous disease, since the only conditions under which surgical treatment is permissible are those in which one can be absolutely sure of removing the tuberculous lesion in its totality. This makes it highly important that tuberculous vesiculitis be correctly diagnosed in its earliest stages.

Carcinoma.—McNally and Cochems [70] stated that 16 instances of primary carcinoma of the seminal vesicles have been reported in the literature, of which only 4 were definitely proved. In the case reported by these authors, the chief complaint was hematuria. The diagnosis of primary carcinoma of the right seminal vesicle was made on the basis of hematuria and a hard mass in the right seminal vesicle. The tissues were radically excised, and the clinical diagnosis was confirmed by the histologic examination of the tissue removed. The prostate gland was later removed and found to be free from carcinoma. An additional interesting histologic observation was the presence of tuberculosis. In the excised prostatic tissues were lesions of tuberculosis, apparently a latent activated infection associated with an old tuberculosis of the spinal column. The patient is free from clinical evidence of recurrence or metastasis more than two years after operation. This seems to be the only case of primary carcinoma of the seminal vesicle on record in which the patient was alive and free from symptoms two years after radical excision.

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[70] McNally, Andrew, and Cochems, F. M.: Primary Carcinoma of the Seminal Vesicles, J. Urol. **36**:532-537 (Nov.) 1936.

TESTES

Undescended Testes.—Hess, Kunstadter and Saphir[71] stated that the determination of the gonadotropic hormone in the urine of 13 boys who had cryptorchidism revealed the presence of significant amounts of the hormone in the urine of 5. These data are consistent with the belief that in the latter cases the condition resulted from a failure of the gonadal mechanism, the pituitary body being functionally active. The patients responded to treatment with gonadotropic substance by descent of the testes and disappearance of the hormone from the urine.

In 3 cases of unilateral cryptorchidism in which the descended testis was apparently normal there was no increase in the excretion of gonadotropic hormone prior to treatment, and only 1 of the 3 patients responded to treatment by descent of the other testis.

In 2 of the 5 cases of bilateral cryptorchidism in which there was no gonadotropic hormone before treatment and in which treatment with gonadotropic substance was not successful, primary pituitary dysfunction was diagnosed, as there was clinical evidence of infantilism in each case.

The authors were of the opinion that if the results in their series of cases are substantiated by future observations there is indication of a possible sphere of usefulness for the determination of the urinary gonadotropic hormone in expressing the prognosis in case of cryptorchidism in which treatment is being given. The presence of the hormone in the urine justifies medical treatment and offers a favorable prognosis in the absence of mechanical obstruction.

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[71] Hess, J. H.; Kunstadter, R. H., and Saphir, William: Urinary Excretion of Gonadotropic Hormone in Cryptorchidism, J. A. M. A. **108**:352-354 (Jan. 30) 1937.

TUNICA VAGINALIS

Hydrocele.—In 23 cases in which there were 25 hydroceles a cure was obtained in all except 1 case.[72] The patients were followed from one to forty-eight months, the average period being seventeen and three-tenths months. There were 2 examples of bilateral hydroceles. with complete cure in each case. The smallest hydrocele had a capacity of 5 cc. and the largest 1,400 cc.; the average capacity in cases in which a cure was obtained was 187 cc., which should be an indication that size is no contraindication to this type of therapy. The youngest patient was 6 years of age, and the oldest was 77 years; the average age in the cases in which the age was given was 50.4 years. From one to four injections were required; an average of two and four-tenths injections were employed in the cases in which a cure was obtained.

URINE

Anuria.—In an effort to explain the problem of reflex anuria, Uebelhör [73] studied the renorenal reflexes by direct visual observation of the renal capillary system. Changes were observed in rabbits and in guinea-pigs which can be compared with the pathologic process in man. The existing theory that reflex anuria arises in the healthy kidney by a sudden ischemia caused by injury of the other kidney is possible. By chemical examples Uebelhör indicated the variation of the causes of anuria. He reported several cases which support his theory and make the origin of true reflex anuria easier to understand. Often, in cases of so-called reflex anuria, causes other than a reflex mechanism can be found to explain the anuria. The author discussed the morphologic findings in cases of anuria and showed that a careful microscopic examination of the kidneys sometimes may disclose the cause of the condition.

Root [74] stated that anuria may occur in cases in which the patient has only one kidney and be associated with infection of mild degree, especially if a loss of base and chloride occurs as a result of vomiting, sweating or diarrhea. Intravenous administration of physiologic solution of sodium chloride in sufficient quantity may produce relief even after ninety-six hours of anuria. The injection of hypertonic saline solution may be necessary. The use of solutions more concentrated than 10 per cent may cause a chill and is contraindicated. The administration of salt in the form of liquid, such as broth, or as tablets i-to be borne in mind in cases in which water and chloride are being lost during excessive sweating, diarrhea or vomiting.

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[72] Mayers, M. M.: Treatment of Hydrocele and Similar Scrotal Cysts by the Injection Method, J. Urol. **37**:308-318 (Feb.) 1937.

[73] Uebelhör, Richard: Die reflektorische Anurie, Arch. f. klin. Chir. **187**: 389-413 (Jan.) 1937.

[74] Root, H. F.: The Intravenous Administration of Hypertonic Salt Solution for Anuria in Patients with One Kidney, J. A. M. A. **108**:947-949 (March 20) 1937.

Amicrobic Pyuria.—Wildbolz[75] stated that cases of amicrobic pyuria have been observed in Europe for a longer period and much more frequently than in the United States and are the object of eager research. Faltin, before the Eighth Congress of the Northern Surgical Society, in Helsingfors, in 1909, was the first to state that he had observed cases of pyuria in which he was unable to find any micro-organisms in the purulent urine, either by microscopic examination or by culture, and in which tuberculosis could be excluded.

Amicrobic pyuria is of great clinical importance. It is easily curable by medication but is often mistaken for tuberculosis of the urinary tract. As a result of such mistakes, nephrectomy has been performed unnecessarily on a number of patients. Therefore, it is important to make the clinical picture of amicrobic pyuria as widely known as possible. There are two types of amicrobic nontuberculous pyuria: a terminal stage of a urinary infection primarily caused by such an organism as Bacterium coli, the staphylococcus or the streptococcus, and primary amicrobic pyuria.

The first form of sterile pyuria is not rare. Its origin may easily be understood by comparison with similar processes elsewhere. Just as gonorrheal urethritis leaves purulent secretion for a long time after all gonococci have disappeared, infection of the upper part of the urinary tract may leave pyuria after all pyogenic bacteria have gone.

The pathogenesis of the second form of sterile pyuria, primary amicrobic pyuria, is not yet clear. Wildbolz has been unable at any time to find bacteria in the purulent sediment by microscopic examination or by culture. Primary amicrobic pyuria usually sets in acutely, with marked vesical symptoms, urinary urgency and tenesmus and painful micturition. There is no fever and no constitutional disturbance. The urine is purulent and generally contains erythrocytes. Sometimes there is sufficient blood in the urine to be noticed by the patient shortly before death. Cystoscopy shows that the vesical mucosa is reddened in patches and discloses ecchymoses and mucopus in the form of stripes or round white necrotic membranes. There is pus in the urine from one or both kidneys on ureteral catheterization. It is characteristic of amicrobic pyuria that in spite of this renal pyuria one never finds a marked decrease in renal function. Amicrobic pyuria usually is observed in young men and rarely in women.

Schaffhauser succeeded in a few cases of typical amicrobic pyuria in growing nonhemolytic streptococci on Rosenow's bouillon; cultures were positive on this medium alone. Growth was slow; colonies were visible only after from three to four days. It is remarkable that this

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75. Wildbolz, Hans: On Amicrobic Pyuria, J. Urol. **37**:605-609 (May) 1937.

streptococcus when transferred to the urinary tract of dogs reproduced in them clinical and pathologic changes similar to those of amicrobic pyuria of man.

Wildbolz stated that a few intravenous injections of an arsphenamine will cure amicrobic pyuria promptly, even when the patient has suffered for months and years from pyuria which has resisted all other therapeutic efforts. Usually one or two injections of 0.15 Gm. of neoarsphenamine are enough to obtain a prompt cure.

Urinary Salts.—Among the important factors affecting the solubility of insoluble salts are the degree of acidity and the neutral effect of the neutral salt. Sisk and Toenhart[76] stated that the importance of acidity is more generally recognized than that of the effect of the neutral salt; however, both are important and both may be applied clinically. The solubility of calcium oxalate is not materially affected by the normal range of acidity encountered in urine, but it is appreciably affected by the neutral salts present.

That the solubility of the insoluble salts is affected by the small amount of colloids present in urine has not been demonstrated, and Sisk and Toenhart found no difference in the solubility of calcium oxalate in a solution of urinary colloids as compared with water. That urinary colloids retard precipitation from a supersaturated solution is yet to be established. That the urinary colloids lower the surface tension of the urine has been established. In doing so, it has been suggested that the surface tension of the urine is brought to the same level as that of the normal mucous surfaces of the urinary tract. In maintaining the state of supersaturation of urine until it is voided, the element of time is important. This explains in part at least the association of stasis and stone, even when the urine is normal. Some dyes retard the precipitation of salts from supersaturated solution.

It is certain that precipitation of a compound will not occur unless the solubility of that compound had been exceeded. A knowledge of the factors influencing solubilities in urine is necessary if one hopes to approach the problem of sediment and stone formation in the urinary tract.

UROLOGIC COMPLICATIONS OF CARCINOMA OF THE CERVIX

In a large series of cases of carcinoma of the cervix which Graves, Kickham and Nathanson[77] studied clinically and at necropsy with reference to changes in the upper part of the urinary tract, obstruction of the ureters was encountered in more than 70 per cent. Because of this high incidence of ureteral occlusion, which has been confirmed by other writers on this subject, it is urged that complete urologic investigation be included in the management of this disease. As has been shown, both diagnosis and prognosis will thus be rendered more accurate, and measures of relief may be made available for the pain and distressing symptoms of uremia which so often confront the patient. It was the opinion of the authors that the urologist may find in this difficult problem a new and highly important field of usefulness.

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[76] Sisk, I. R., and Toenhart, Otto: Factors Influencing the Solubility of Relatively Insoluble Salts in Urine, J. Urol. **37:**595-603 (April) 1937.

[77] Graves, R. C.; Kickham, C. J. E., and Nathanson, I. T.: The Ureteral and Renal Complications of Carcinoma of the Cervix, J. Urol. **36:**618-640 (Dec.) 1936.

UROLOGIC COMPLICATIONS OF UTERINE AND OVARIAN TUMORS

Morris and Juracsek[78] made a complete urologic examination of 43 females with tumors which originated in the reproductive tract; 76 per cent had symptoms referable to the urinary tract. In 44.2 per cent ureteral dilatation was demonstrable, and in 37 per cent there was dilatation of the renal pelvis. Symptoms referable to the renal region were present in only 50 per cent of the patients in whom hydronephrosis was demonstrated. Sixty per cent of the tumors which did not rise to the level of the umbilicus produced a variable degree of dilatation of the ureters or renal pelvis. Fifty per cent of the tumors which rose above the level of the umbilicus produced dilatation of the ureters or renal pelvis.

HYDATID CYSTS

Imbert,[79] who made a study of the pyelographic images formed by open and closed hydatid cysts of the kidney, stated that in the presence of a closed cyst pyelography may show a normal image, deformation of the pelvis and calices, amputation of the pelvis and calices or displacement of the ureter; in the presence of an open cyst it may reveal the cystic pocket filled with the opaque substance, and it practically always will show some enlargement of the ureter due to passage of daughter cysts and blood clots. The pyelogram may show definite lacunae; there may be clear zones in the midst of opaque regions in the injected pocket.

The hydatid cyst is rather well adapted for diagnosis by pyelography, since this frequently shows the rounded shadow of the cyst compressing some of the calices. Frequently it is desirable to make two roentgenograms, one before and the other after the opaque fluid has displaced the abdominal mass. An open cyst with a calcified adventitia is rather easily recognized in the pyelogram by the regularity of its contours. It is difficult to distinguish between a hydatid cyst and a solitary cyst; in the presence of an open hydatid cyst, the image of the daughter cysts may be decisive for diagnosis. Bilaterality of the deformation will easily eliminate polycystic kidney. The "spider" form of renal tumor is clearly distinguished from the rounded contours of a hydatid cyst.

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[78] Morris, H. L., and Juracsek, Valeria R.: Involvement of the Upper Part of the Urinary Tract Associated with Uterine and Ovarian Tumors, J. Urol. **37**:582-587 (April) 1937.

[79] Imbert, Marc: La pyélographie dans les kystes hydatiques du rein, Arch. d. mal. d. reins **10**:153-165 (March) 1936.

As regards the location of the cyst, Imbert stated that pyelography gives precise indications. Thus, a hydatid cyst of the upper pole, acting by force of gravitation, lowers the kidney and produces a zigzag kink of the ureter and an amputation of the superior calix. When the cyst is open, the opaque substance fills the cavity, which then assumes the form of a more or less dilated balloon. If the cyst is in the middle third of the kidney, it will cause the middle calix to disappear, will compress the pelvis and will stretch out the superior and inferior calices and produce a "crescent" appearance. If it is at the lower pole, it will displace the kidney upward and force the ureter to take a regularly rounded curve following the outline of the cyst; this can be recognized in either the frontal or the profile position. The renal pelvis may then become a horizontal line; the inferior calix is frequently amputated, and the compression provokes a hydronephrosis.

Pyelography is thus a guide to the correct mode of operative approach and enables the surgeon to choose a route that will prevent unnecessary destruction of renal parenchyma. For a cyst of the upper pole the lumbar incision should always be employed, since it permits adequate operative exposure, especially after resection of the twelfth rib. This method is also applicable for a cyst of the middle third of the kidney or even for a cyst of the lower pole if the extension is into the abdominal cavity. Pyelography also will indicate whether or not the operation should be conservative. The author cannot agree with Racic, who said that pyelography does not permit a diagnosis more than once in 13 cases. Two views, frontal and profile, should always be taken, before and after filling. Retrograde pyelography should always be employed; a catheter should be placed in the ureter to maintain its normal form without straightening out its pathologic curvatures.

INFECTION OF THE URINARY TRACT

Sewell, Kasper and Broom[80] reported a case in which the results of bacteriologic and histologic examinations of the kidney indicated that chromogenic acid-fast bacilli may be pathogenic for man and may be capable of causing changes in the tissues likely to be confused with those caused by infection by the tubercle bacilli. An error in diagnosis may result if such organisms are studied only by means of the direct smear or if reliance is placed on animal inoculation for the diagnosis. Pinner has demonstrated that inoculation of animals with chromogenic acid-fast bacilli will result in the development of lesions, which may disappear by the end of the period usually required for the development of tubercles.

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[80] Sewell, George; Kasper, Joseph, and Broom, Norma: Chromogenic Acid-Fast Bacillus Infection of the Urinary Tract, J. Urol. **37**:385-393 (March) 1937

Since the pathogenicity of some, at least, of the chromogenic acid-fast bacilli is established, caution should be exercised when reporting the results of direct microscopic examination of cystoscopic or simple catheterized specimens of urine. Otherwise, an erroneous diagnosis of tuberculosis might be the result.

The true nature of the chromogenic acid-fast bacilli has not yet been determined. Further work is now in progress to learn if they are related to tubercle bacilli. In a series of 130 specimens of sputum obtained from known tuberculous patients, 34 of which gave positive cultures, approximately 20 per cent were found to contain chromogenic organisms.

Although nephrectomy was performed for the complete relief of symptoms in the case which was reported, it is probable that in similar cases in which there is less extensive involvement of the urinary tract the patient may recover spontaneously. The animal experiments of Pinner and those in the authors' laboratory tend to support this view.

URINARY ANTISEPSIS

Cook[81] stated that the oral administration of synthetic racemic beta-hydroxybutyric acid causes definite increase in urinary excretion of this substance when the patient to whom the drug is given is in a state of sufficient ketosis. There is no change when the substance is given to a patient who displays little or no ketosis.

The local use of a 2 per cent solution of beta-hydroxybutyric acid buffered to a p_H of from 4.4 to 4.5 has proved beneficial in those cases in which the results with the diet have been unsuccessful or the patient has been unable to stand the dietary regimen. Seven of the ten patients so treated gave negative urinary cultures. In 2 of the remaining 3, symptoms were markedly relieved, while in 1 no benefit was obtained.

The sodium salt of beta-hydroxybutyric acid when given orally will produce an increase in urinary excretion of the acid, but apparently, to a less degree than oral administration of the pure acid.

The calcium salt of beta-hydroxybutyric acid was given intravenously in 3 cases. In none of these was an appreciable change noted in the urinary concentration of the acid.

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81. Cook, E. N.: The Use of Beta Hydroxybutyric Acid and Certain of Its Salts as an Adjunct in the Treatment of Infections of the Urinary Tract. J. Urol. **36**:289-297 (Sept.) 1936.

Buchtel and Cook[82] reported that according to replies to questionnaires from 161 patients who had bacillary infections of the urinary tract and who had been treated by means of the ketogenic diet on an average of two years previously, 26 per cent had recurrences. There was little difference in the incidence of recurrence of the various bacilli. In the majority of cases the recurrence was mild and occurred within the first three months. A ketogenic diet suitable for use in the home was outlined. The ketogenic diet is a successful method of treatment, not only in regard to the immediate results but also in regard to end-results.

HYPERPYREXIA

Potter, Redewill and Longley[83] discussed various agents for producing therapeutic fever. Physical agents used for the production of therapeutic fever are of two classes: those operating in a medium higher than the body temperature and those operating in a medium lower than the body temperature. The former are not considered physiologically as desirable as the latter. The biophysical action of the latter, with which the heat is generated in the body, the lessened shock-producing elements involved, the added comfort of the patient and the consistently lower pulse rate that occurs when prolonged high temperatures are maintained by application of electromagnetic induction in the cool cabinet make their use the method of choice.

Hyperpyrexia may prove dangerous or fatal unless given by skilled operators, and the mismanagement in cases of emergencies has done much to bring it into disrepute.

One hundred and eighty-nine cases of gonorrheal infection and complications were reported; 1,001 hyperpyrexia treatments were given with the inductotherm and the Kimble cabinet. The results were most striking in cases of gonorrheal arthritis. However, all types of gonorrheal infection except chronic posterior urethritis responded satisfactorily to fever therapy. In the 1,001 treatments given with hyperpyrexia, only 3 serious reactions developed (heat collapse), and there were no fatalities.

Active chemotherapy in the form of intravenous injection of dextrose and mercurochrome seems to aid the therapeutic effect of hyperpyrexia.

The production of therapeutic fever with the electromagnetic induction in the Kimble cabinet has added greatly to the urologist's armamentarium.

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[82] Buchtel, H. A., and Cook, E. N.: End-Results of Treatment of Urinary Infections by the Ketogenic Diet, Minnesota Med. **19**:603 (Sept.) 1936.

[83] Potter, J. E.; Redewill, F. H., and Longley, E. G.: Hyperpyrexia as an Adjunct in Treatment of Non-Surgical Urological Conditions, J. Urol. **37**:214-225 (Jan.) 1937.

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NONSPECIFIC MESENTERIC LYMPHADENITIS

REPORT OF SEVENTY-FIVE CASES

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Mesenteric lymphadenitis is by no means a new pathologic entity. Much has been written about in in recent years. However, as a clinical entity it is unknown or frequently forgotten by a large group of medical men as well as surgeons. I present this article in order to emphasize the fact that this disease occurs in everyday practice, and often just keeping it in mind allows one to explain an otherwise baffling array of symptoms. When one is on the lookout for this disease entity (if I may call it such), one may be rewarded by makin a correct diagnosis, the verification being made at the operating table.

I am especially interested in mesenteric lymphadenitis from the point of view of: (1) diagnosis, which is often obscure; (2) etiology, which is still in doubt, and (3) treatment and prognosis.

My experience and that of authors whose writings have been consulted have led me to use the following clinical classification for this disease: (1) chronic mesenteric lymphadenitis, (2) acute mesenteric lymphadenitis, (3) acute fulminating mesenteric lymphadenitis and (4) acute suppurative mesenteric lymphadenitis.

Before discussing these various forms, I should like to stress the fact that this is not a pathologic classification but a clinical one based on history, physical examination and operative findings.

Under chronic mesenteric lymphadenitis are included cases in which the patient comes to operation for so-called chronic appendicitis. Usually there is chronic recurrent pain in the right lower quadrant, which may be vague in distribution or localized to the right side. The monotony of indefinite abdominal pain may be broken by acute exacerbations, often related to an infection of the upper respiratory tract, acute tonsillitis or cervical adenitis. There may or may not be associated gastro-

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Read at the bi-monthly meeting of the staff of the Montefiore Hospital, Sept. 29, 1936.

From the Landon Service Department of Surgery and the Isaac Kaufman Foundation of the Montefiore Hospital.

intestinal symptoms—more often they are minimal. The temperature and pulse rate may be slightly elevated, if at all, and the same might well be said of the white cell count. Physical examination will usually show a point of tenderness in the right lower quadrant of the abdomen, with no rigidity. A point has been described slightly above and medial to McBurney's point as a maximum area of tenderness. In my experience this point of maximum tenderness is of variable position, and I think it sufficient to say that there is tenderness in the right lower quadrant.

If the patient is operated on at a time when he is relatively free from symptoms, the appendix will be found to be grossly normal; and if the mesentery is inspected, it will be found studded with enlarged glands in the ileocecal region, the size varying from that of a pea to that of a kidney bean and increasing toward the root of the mesentery.

Anatomists say that glands in the ileocecal region vary from one hundred to one hundred and fifty in number, there being two paths of flow—one toward the mesenteric glands and the other retroperitoneally along the ascending colon. One may voice the objection that it is a fairly normal state of affairs to find enlarged glands in the mesentery. That this is not so is attested to by the fact that any number of times I have inspected the mesentery at various types of laparotomy and have not been able to see or palpate mesenteric glands. Moreover, Mead[1] has shown in a rather exhaustive study of an extensive series of autopsies that mesenteric glands which can be seen and palpated by the examining finger are definitely an abnormal finding.

The usual procedure in this type of case is to remove the appendix, and the usual liberal pathologic report of chronic appendicitis is made. If one of these glands is removed for pathologic section and culture, the examination will show hyperplasia and the culture will be negative. Figure 1 is a photomicrograph of a section taken from one of these glands. The pathologic report as rendered by Dr. K. Yardumian is as follows:

Gross Description: The specimen consists of a lymph node the size of a split pea, fairly firm in consistency. The capsule is intact. It is rather pale gray. On section the capsule is slightly thickened and has a smooth pinkish gray surface.

Microscopic Description: Sections show moderate thickening of the capsule with a slight increase of trabeculae and advanced hyperplasia of the reticulum cells with replacement of areas of lymph tissue by reticulum cells. The sinusoids are filled with endothelial leukocytes. No mitosis is present.

Diagnosis: Chronic toxic lymphadenitis (nonspecific).

The second type, which I have arbitrarily called the acute variety, merges insensibly into the first. There may or may not be an antecedent history of acute abdominal pain. The pain may be identical in nature and distribution with that of acute appendicitis. Often, however, it is more colicky, this being explained on a basis of intestinal spasm secondary to irritation in the mesenteric root. The radiation of pain is usually to the right lower quadrant. Nausea is present as a rule, but emesis is not so frequent. The temperature varies from 99 to 101 F., and the pulse is generally accordingly increased. The patient does not appear very ill, but physical examination shows definite tenderness in the right lower abdominal quadrant, with some spasticity. Some rebound tenderness may be present, and peristalsis is usually normal or even somewhat exaggerated. The white cell count is generally elevated, and the polymorphonuclear count varies from 65 to 90 per cent. This is the type of case in which the surgeon is called in consultation and, after going into the history and examining the patient, announces that he does not believe that the patient has acute appendicitis. However, he is unable to rule it out definitely, and a laparotomy may or may not be performed, depending on the surgical principles by which he abides. At

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[1] Mead, Charles: Mesenteric Lymphadenitis Simulating Acute Appendicitis: Quantitative Study of Size of Normal Mesenteric Lymph Nodes, Arch. Surg. **30**:492-527 (March) 1935.

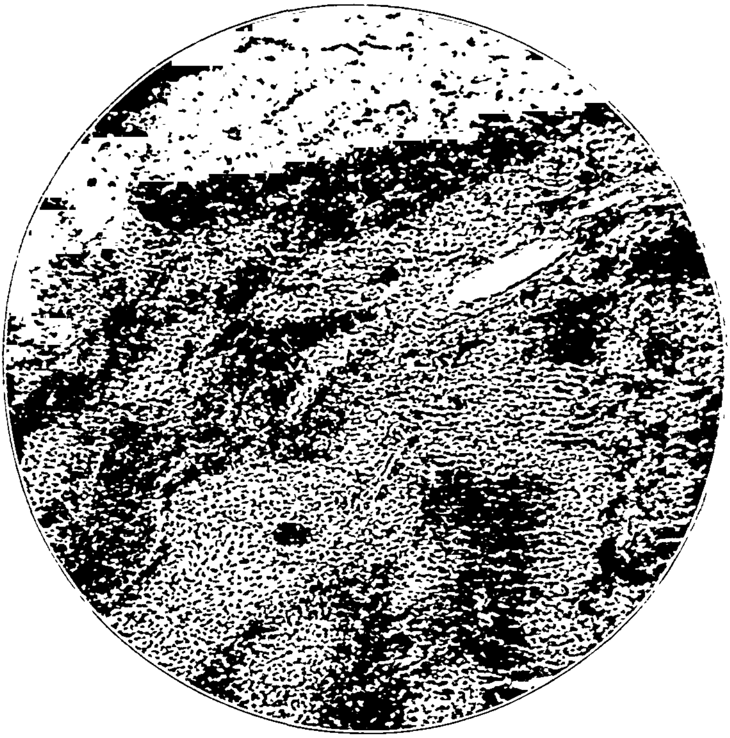

Fig. 1.—Microscopic section of a gland removed in a case of chronic mesenteric lymphadenitis.

operation the appendix is found to be normal, but the mesentery is studded with swollen glands reaching the size of an almond. Postoperatively, the temperature gradually approaches normal, and convalescence is thereafter usually uneventful. Figure 2 shows the temperature charts in three typical cases of acute mesenteric lymphadenitis.

If a gland is removed for section and culture, the culture will be negative and the gland will show acute hyperplastic changes. A diagnosis of chronic appendicitis is usually made. Figure 3 is a photomicrograph of a section taken from a gland removed in a case of acute mesenteric lymphadenitis. The following report on this section was rendered by Dr. K. Yardumian:

Gross Description: The specimen consists of a lymph node the size of a navy bean. The capsule is intact. It is soft in consistency and hyperemic. On section, it is pinkish gray, with discrete opaque areas.

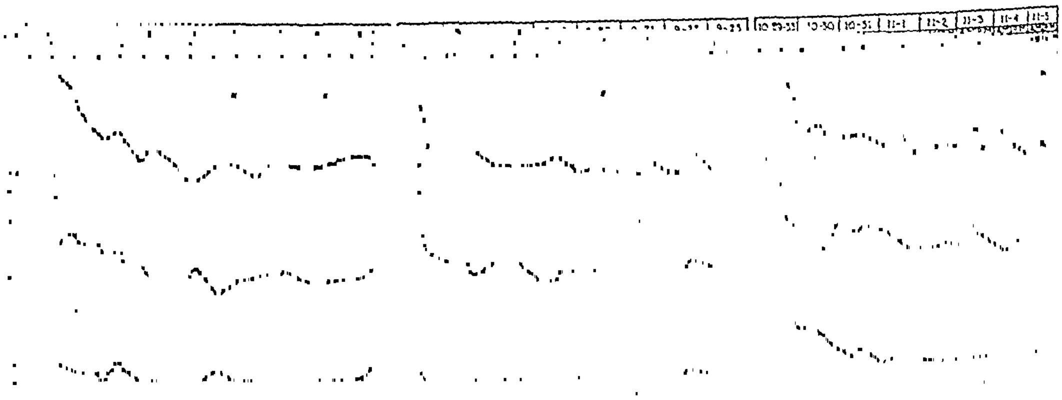

Fig. 2.—Temperature charts in three typical cases of acute mesenteric lymphadenitis.

Microscopic Description: Sections show moderate hyperplasia of the germinal centers with a few mitotic figures and thinning out of the lymphocytic zone. There are dilated capillaries and sinusoids with areas of extravasation of blood and moderate proliferation of the reticulum cells. No polymorphonuclear infiltration is seen, and there is no evidence of a specific inflammatory reaction.

Diagnosis: Acute toxic lymphadenitis (nonspecific).

The third type of mesenteric lymphadenitis, which I have chosen to call acute fulminating mesenteric lymphadenitis, presents a very different picture. It is impossible to differentiate this condition from rapidly advancing acute appendicitis. As a matter of fact, the picture is so overwhelmingly that of an acute abdominal catastrophe that one does not even consider a diagnosis of acute fulminating mesenteric lymphadenitis. The patient is usually a child and presents the picture of an acute toxic state. The story is one of diffuse abdominal pain, generally localizing in the right lower quadrant and associated with protracted emesis. The face is flushed, breathing is rapid, and the tongue is coated and dry. Examination of the abdomen reveals diffuse tenderness in both the right and the left lower quadrant, with a variable amount of rigidity. Rebound tenderness is usually exquisite, even in the left lower quadrant. Abdominal peristalsis is absent or greatly diminished. The temperature varies from 101 to 103 F., and the pulse is rapid and bounding. The white cell count is high, hovering around 20,000, with a high percentage of polymorphonuclears. All in all, one gives the patient a rather guarded prognosis on the basis that he has acute appendicitis with peritoneal contamination. On opening the abdomen one finds a fair amount of clear to slightly cloudy fluid, accounting no doubt for the pain on the left side. Culture of this fluid will be found to be negative. The small and large intestines, including the appendix, will show diffuse injection. Otherwise, to the surgeon's great surprise, the appendix is practically normal. The mesentery, however, is studded with acutely swollen glands, which give one the impression of wanting literally to pop out of the mesenteric leaves.

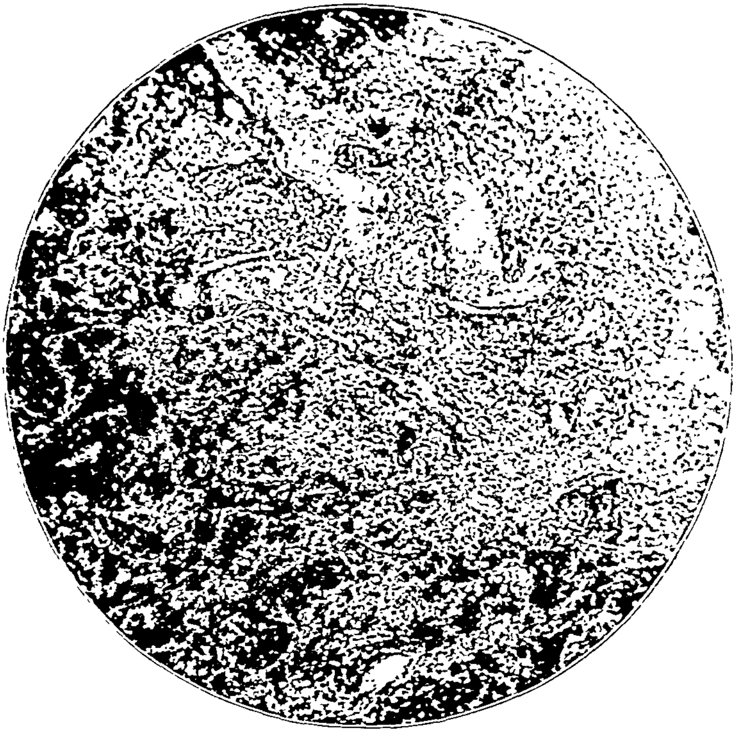

Fig. 3.—Microscopic section of a gland removed in a case of acute mesenteric lymphadenitis.

Some men have described an exudative process in the peritoneal cavity in connection with the acute process in the mesenteric glands. I have not encountered this type as yet. In one of the cases I found what I have chosen to call acute hemorrhagic mesenteric lymphadenitis. Besides the aforementioned swelling of the glands, I noted diffuse hemorrhages throughout the glands. Postoperatively, the patient with acute fulminating mesenteric lymphadenitis is quite ill for a few days, the temperature gradually seeks normal and convalescence is soon firmly established. Figure 4 is a temperature chart illustrative of this type of case.

It has been my good fortune to date not to encounter the fourth type, namely, acute suppurative mesenteric lymphadenitis. However, in such cases one or more glands go on to suppuration, with resultant spreading peritonitis or abscess formation. Whether this entity is the late result of the other forms which I have described, I am not prepared to state. Suffice it to say that the picture is one of acute peritonitis with resultant diffuse spread or abscess formation. The prognosis in the former is very grave, and that in the latter is more favorable as to ultimate recovery.

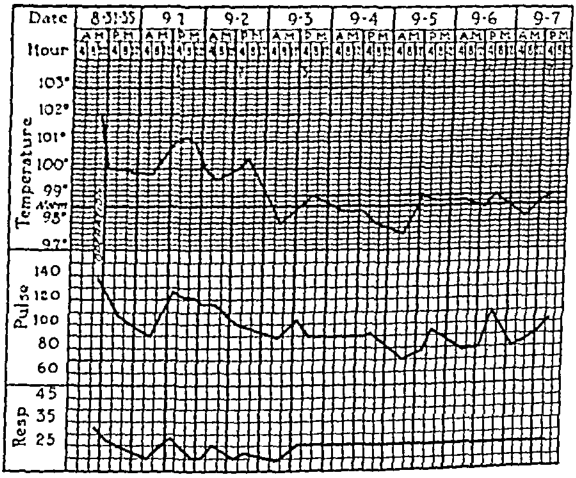

Fig. 4.—Temperature chart in a case of acute fulminating mesenteric lymphadenitis.

DIAGNOSIS

At the beginning of this article I stated that I was especially interested in three phases of this entity.

The first of these is diagnosis. I might go on at length and outline all the various diseases which might be confused with mesenteric lymphadenitis, varying all the way from ureteral calculus to ordinary gastroenteritis. However, practically speaking, the diagnosis of the chronic variety of mesenteric lymphadenitis presents the same problem as the diagnosis of chronic appendicitis. Involvement of the urinary tract, the pelvic organs and the genito-urinary tract must be ruled out. Then one is confronted with the question of whether the condition is chronic appendicitis or chronic mesenteric lymphadenitis. A history of attacks related to infections of the upper respiratory tract may help in diagnosis. As the criteria for a diagnosis of chronic appendicitis (even in the pathologic laboratory) are rather vague, the question as to whether the appendix or the glands (when found at operation) are at fault still remains in abeyance. Even the problem as to whether the enlarged glands do or do not result from chronic appendicitis must necessarily evade settlement at the present time.

In the acute variety it is the differential diagnosis from acute appendicitis which is of main concern. I am loath to admit that as yet I have been unable to settle on any real practical differentiating point. It is needless to go into detail concerning the various points in the history and physical examination, because I am ultimately left with the following dictum: If one cannot rule out acute appendicitis the abdomen must be opened. I have tried the sedimentation test as a means of differentiation, only to find that it is of no real value in this type of case, the sedimentation time being long in both the ordinary case of acute noncomplicated appendicitis and the ordinary case of acute mesenteric lymphadenitis. Recently, I utilized the Schilling index in the differential diagnosis of the acute abdominal condition, but in my hands it has been of no great value, especially in the dubious case. The only statement I feel justified in making is as follows: When one encounters a patient who presents an atypical picture of acute appendicitis, especially when there is a history of an acute infection of the upper respiratory tract, acute mesenteric lymphadenitis should be kept in mind.

As to the acute fulminating and acute suppurative types, I do not believe it possible even to consider a differential diagnosis.

ETIOLOGY

The etiologic factor in this disease is one on which authorities have not agreed. I have chosen the term nonspecific because I believe that in the great majority of cases I am dealing with a nontuberculous factor. I do not deny that there is such an entity as tuberculous mesenteric lymphadenitis, but it is my opinion that the cases reviewed here are predominantly of a nonspecific variety. *In this opinion I am supported* by Wilensky,[2] Hahn[3] and others. Some authors have injected excised mesenteric glands into guinea-pigs, with from 20 to 40 per cent positive

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2. Wilensky, A. O.: M. Rec. **98**:770 (Nov. 6) 1920.
3. Wilensky, A. O., and Hahn, L. J.: Ann. Surg. **83**:812-826 (June) 1926.

results for tubercle bacilli. These studies form the basis for the belief which one school holds that mesenteric lymphadenitis is tuberculous in the greatest percentage of cases.

The difficulty in proving the etiologic factor lies in the facts that these cases are usually not fatal and that surgeons are loath to (and rightly so) remove a mesenteric gland because of danger to important intestinal vessels in the mesentery. However, some men have removed glands for study. The results of microscopic section in my series of six glands have failed to show any histologic evidence of tubercle formation. Inoculation of guinea-pigs was not carried out because of insufficient material.

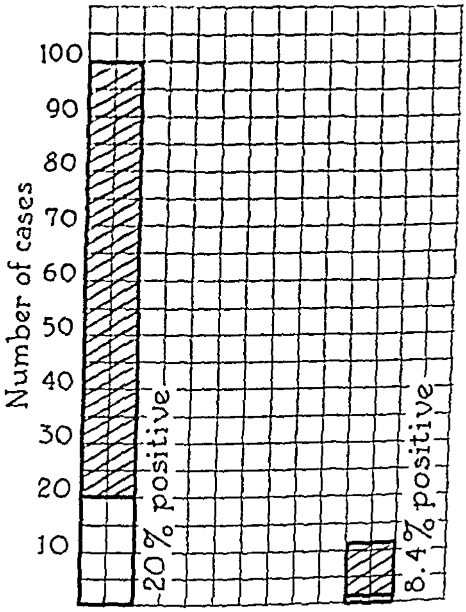

Fig. 5.—Chart showing the results of tuberculin tests in one hundred routine cases and twelve cases of mesenteric lymphadenitis.

In an attempt to disprove the tuberculous etiology, I thought that a comparison of the results of *tuberculin* tests in a series of cases of mesenteric lymphadenitis with those in a series of routine cases observed at the hospital might be of value. It is my conception that if mesenteric lymphadenitis does have a tuberculous basis one could certainly expect a much higher percentage of positive reactions in the former series of cases than in the latter. The following has been my experience: In a series of twelve cases of mesenteric lymphadenitis, one positive tuberculin reaction was obtained, giving a percentage of about 8.4 per cent. In a series of one hundred routine cases, sixty of which were cases of abdominal conditions, there were twenty positive reactions, or 20 per cent. Figure 5 shows these results.

I fully realize that the series is small, perhaps too small, to permit drawing of conclusions. However, there is no mistaking the fact that in the series of cases of mesenteric lymphadenitis there was even a lower percêntage of positive tuberculin reactions than in the series of ordinary cases in which tuberculosis was not suspected. I feel certain that if one performed tuberculin tests in a series of twelve cases of tuberculous cervical adenitis, a high percentage of positive reactions would be obtained. I see no reason why the same should not be true of mesenteric lymphadenitis, assuming that it were on a tuberculous basis.

If the tubercle bacillus is not the etiologic factor, where may one look further for the cause? Goldberg and Nathanson [4] cultured material from the throat in a series of these cases and obtained Streptococcus haemolyticus. Cultures from the glands removed for biopsy showed the same organism in one of eight cases.

In my series of six glands aerobic cultures were performed, and I was unable to obtain growths from any. Anaerobic cultures were run on three of these because I felt that perhaps the organism being possibly absorbed in the gastro-intestinal tract was anaerobic. However, no positive cultures were obtained.

Table 1.—*Results of Laboratory Investigation*

Number of glands removed for biopsy	6
Evidence of tuberculosis	None
Number of glands removed for culture	6
Aerobic culture (sterile)	6
Anaerobic culture (sterile)	3

It is logical to look for the cause in the intestinal tract. I have not been able to demonstrate any lesion, at least from the serosal side. Some authors have visualized a catarrhal enteritis or minute ulceration as the point of entrance for micro-organisms. However, the paucity of gastrointestinal symptoms militates against this assumption. Moreover, in the one fatal case in this series autopsy failed to show any gross evidence of intestinal lesions. I do not feel that the appendix is at fault (although proof of this assumption is not available), because I view with suspicion the diagnosis of chronic appendicitis which is so liberally returned by the pathologist. It might be of interest to state at this point that only rarely in cases of acute appendicitis does one see enlarged mesenteric glands.

It is an established fact that one often sees acute abdominal pain associated with acute tonsillitis and infection of the upper respiratory tract.[5] It is fairly well accepted that this pain is probably on a mesenteric lymphadenopathic basis. How can this spread be explained? One must assume either that it is due to toxic infective products reaching the ileocecal junction and then being absorbed or perhaps that it is spread by the hematogenous route.

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[4] Goldberg, S. L., and Nathanson, I. T.: Am. J. Surg. **25**:35-40 (July) 1934.

[5] Brennemann, J.: "Abdominal Pain of Throat Infections in Children," and Appendicitis, J. A. M. A. **89**:2183-2186 (Dec. 24) 1927; Abdominal Pain of Throat Infections, Am. J. Dis. Child. **22**:493-499 (Nov.) 1921.

Within the past few years a well known epidemic of meningo-encephalitis occurred at Windber, Pa. According to reports obtained from Dr. H. Schlesinger,[6] the onset was marked by a red granular throat, and a large percentage of the children complained of pain in the right lower abdominal quadrant, which eventually disappeared. The infective agent here was no doubt a virus, and I am of the opinion that investigation of these glands along this line might possibly disclose a virus as the infective agent. It might well explain the negative cultures and the pathologic pictures.

TABLE 2.—*Clinical Observations in Seventy-Five Cases of Mesenteric Lymphadenitis*

	Types of Disease			
	Chronic	Acute	Acute Fulminating	Suppurative
Number	35	38	2	0
Percentage	47	50	3	0

	Sex of Patients	
	Male	Female
Number	20	55
Percentage	26	74

Acute foci of infection	Number of Cases (as Noted on Charts)
Tonsillitis	5
Carious teeth	1
Coryza	2
Cervical adenitis	1
Pharyngitis	1
Suppurative focus in arm	1

From a series of seventy-five cases of mesenteric lymphadenitis, including instances of the chronic, the acute and the acute fulminating form, in which operation was performed at this hospital during the past six years, I have made various observations. Table 2 shows that the acute forms were slightly in the majority. The tabulation of the cases as to sex showed preponderance of females, almost 3 to 1. The presence of an acute focus of infection was noted in only eleven cases.

It is the commonly accepted impression that this disease occurs most frequently in young children. I have no doubt that a great many children as well as adults with mesenteric lymphadenitis are not operated on. In these there is no absolute proof of the diagnosis. However, a

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6. Schlesinger, H.: Personal communication to the author.

tabulation of the seventy-five cases in which operation was performed and glands demonstrated shows the greatest incidence of the disease to be in persons between the ages of 13 and 20. There were no patients operated on below the age of 5. and the minimal number of cases was found in persons between the ages of 5 and 12. Figure 6 shows the results in this age tabulation.

Further study reveals a definite seasonal incidence for this entity. Figure 7 shows the greatest number of cases to have occurred in the months of June to August inclusive and in October to January inclusive. The least number of cases occurred in the period between February and May.

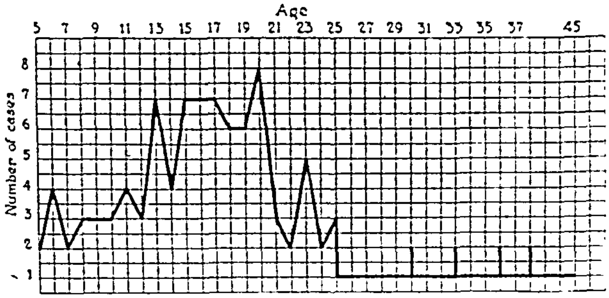

Fig. 6.—Chart showing the age at which mesenteric lymphadenitis occurred.

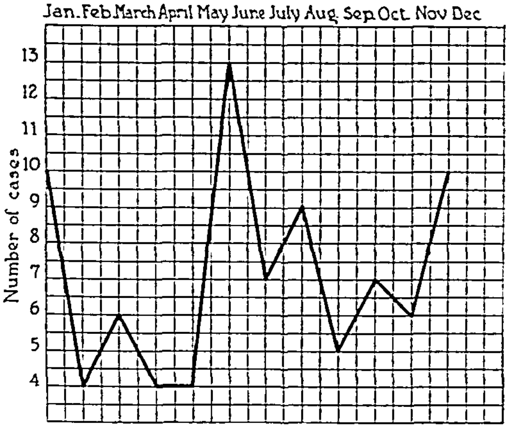

Fig. 7.—Chart showing the seasonal incidence of mesenteric lymphadenitis.

It has been claimed, and perhaps rightly so, that the tonsils are a portal of entry in this disease. I thought that it might be interesting to investigate whether the tonsils and adenoids had been removed previous to laparotomy in these seventy-five cases. I found that twenty-three, or about 30 per cent. of the patients had had their tonsils and adenoids removed. The records stated that they were present in nine. There was no note as to their presence in the remaining forty-three patients. I think it fair to assume that in at least from 15 to 20 per cent of the latter patients the tonsils and adenoids had probably been removed. I state these facts merely to show that the tonsils and adenoids cannot be the offending factor in cases in which they had been previously enucleated. However, I do agree that the remaining lymphatic tissue in the throat or perhaps the teeth could well act as the offending focus.

TREATMENT

Treatment at present is supposedly purely operative, it being assumed that laparotomy in itself results in relief from future pain.

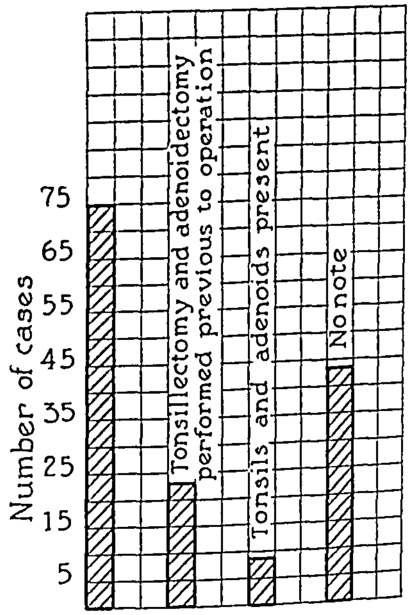

Fig. 8.—Chart showing the results of an investigation as to the presence or absence of tonsils or adenoids in the seventy-five cases of mesenteric lymphadenitis.

Perhaps this is where the impression arises that the etiologic factor is tuberculous, as tuberculous peritonitis is supposed to respond to simple laparotomy. I was not satisfied that laparotomy could result in such a dramatic and permanent cure. Follow-up letters were therefore sent out to the seventy-five patients who were proved to have mesenteric lymphadenitis. These letters were simply phrased as to the presence or absence of abdominal pain and as to the type of abdominal pain which the patient experienced. Replies were received from twenty-nine persons. Of these twenty-nine, ten replied that they had no pain. Ten replied that they had pain similar to their preoperative complaint. The remaining nine still had abdominal pain, but not identical with the pain for which they had been operated on. In other words, nineteen of twenty-nine, or roughly two thirds, of these patients who replied to the inquiries still had abdominal pain of one type or another. This type of follow-up study is not entirely satisfactory in that the last nine patients might well be having pain from abdominal adhesions or some other abdominal factor, but certainly one can get the impression that laparotomy is not the cure-all for these patients' symptoms. I believe that postoperative supportive measures and convalescent care are probably more responsible for relief of symptoms than the simple laparotomy. I think that the liberal use of cod liver oil and ultraviolet radiation and the eradication of foci might well be an important factor in the alleviation of symptoms. At this point, I should like to suggest that roentgen therapy for those persons with persistent symptoms might be worth a trial on the same basis that roentgen therapy is given for cervical adenopathy.[7]

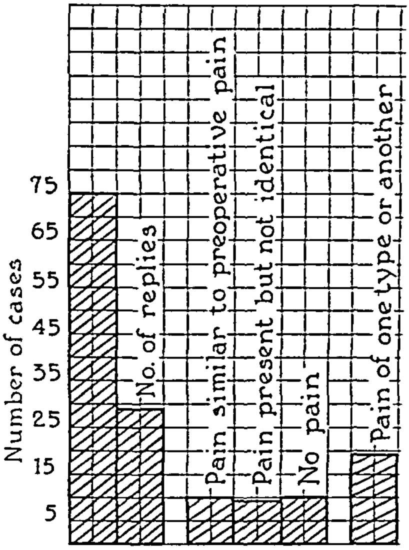

Fig. 9.—Chart showing the results of a follow-up study as to the presence or absence of pain in twenty-nine cases of mesenteric lymphadenitis.

Figure 9 shows the results of follow-up letters as to abdominal pain.

SUMMARY

Nonspecific mesenteric lymphadenitis can be divided into four types, clinically: (1) chronic, (2) acute, (3) acute fulminating and (4) acute suppurative.

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[7] Bell, L. P.: Surg., Gynec. & Obst. **45**:465-473 (Oct.) 1927.

Diagnosis of the chronic type resolves itself into an elimination of other causes of the presenting symptoms. The acute variety is often confused with acute appendicitis, and operation is usually required to decide the issue.

The following conclusions were made concerning the etiology:

(*a*) Tuberculin tests indicated that the tubercle bacillus is not the offending organism.

(*b*) Cultures and sections in six glands failed to show evidence of pyogenic or tuberculous infection.

(*c*) There is a definite seasonal incidence, perhaps related to infection of the upper respiratory tract.

(*d*) Foci of infection are probably important etiologic factors. In twenty-three of seventy-five cases reviewed the patients had undergone tonsillectomy and adenoidectomy previous to operation, thus eliminating the tonsils and adenoids as a source of infection in these cases.

In a series of twenty-nine replies to follow-up letters, two thirds of the patients still had abdominal pain after laparotomy. Postoperative supportive measures are probably of great value in the alleviation of symptoms.

CONCLUSION

In conclusion, I should like to say that nonspecific mesenteric lymphadenitis is a definite entity which can be diagnosed with greater frequency if looked for and kept in mind. I feel that the etiologic factor has yet to be found. Whether the infective agent simultaneously attacks the lymphatic tissue of the respiratory tract and abdomen or secondarily attacks the abdomen with the nose and throat as a focus, it is my impression that focal infection is a more important part of this picture than any theoretical enteric lesion.

I hold no brief against tuberculous mesenteric lymphadenitis, but I feel that the condition seen so frequently at the operating table is in a large percentage of cases of nonspecific origin and should not be laid at the door of the tubercle bacillus.

Dr. Landon, Dr. Schubb and Dr. Frankenstein permitted me to use their records.

SCIATIC SCOLIOSIS

A CLINICAL ANALYSIS OF EIGHTY CASES

MAX A. LEVINE, M.D.
LOS ANGELES

The purpose of this paper is to present the clinical manifestations and results following a uniform type of treatment in the not infrequent complication of pain low in the back, termed "sciatic scoliosis." The theoretical considerations have been thoroughly discussed in another clinical study by Kleinberg.[1]

Briefly, in cases of sciatic scoliosis one has to deal with a lateral curvature of the spine, which most frequently is the result of a derangement (arthritis, sprain, etc.) of the sacro-iliac or sacrolumbar joints, with gluteal myositis or with sciatic neuralgia (sciatic perineuritis). These conditions give rise to pain, which is transmitted along the course of the sciatic nerve. In an attempt to recede from the painful side or area, the patient will unknowingly tilt his trunk laterally and most frequently away from the affected side, producing a functional type of scoliosis. As will be observed later, this is not a true structural scoliosis because of the lack of fixed torsion of the vertebral bodies.

ANALYSIS OF DATA

In the analysis of the etiologic data in eighty cases of sciatic scoliosis it was noted that approximately two thirds of the patients were in the fourth and fifth decades; that there was a conspicuous absence of persons in the first decade, and only an occasional patient in the second, sixth and seventh decades (table 1). The frequency as to sexes was 3:1, the males predominating. Occupations were varied. Among the males, salesmen, printers and chauffeurs were most frequently affected, while among the females, housewives predominated. There was a noteworthy infrequency of the condition among those who did hard labor, possibly because the exercise attendant on their work led to better muscular development. Severe trauma was a predisposing factor in approximately one third of the cases, while mild trauma was contributory in about one eighth. As has been noted previously,[1] infection of

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Orthopedic Service of Dr. Samuel Kleinberg.

From the Hospital for Joint Diseases, New York.

[1] Kleinberg, S.: Sciatic Scoliosis Due to Low Backache, Am. J. Surg. **7**: 89-94, 1929.

the upper respiratory tract will not infrequently predispose to this condition, as it was the factor in one eighth of the cases.

Backache due to derangement of the sacro-iliac or lumbosacral joints, which was the exciting cause in the irritation of the sciatic root, came on abruptly in over two thirds of the patients, and in the remaining one third there was an insidious onset. About one third of the patients gave a history of recurrent pains in the back, while the remaining two thirds were affected for the first time. These attacks occurred intermittently for from four days to twenty years.

TABLE 1.—*Etiologic Data in Eighty Cases of Sciatic Scoliosis*

	Cases	Percentage
Number of patients according to decades (age 16-65, average 35.7)		
First	0	
Second	6	7.6
Third	12	15.2
Fourth	33	42.3
Fifth	20	25.6
Sixth	6	7.6
Seventh	1	1.1
Unmentioned	2 adults	
Sex		
Males	62	77.5
Females	18	22.5
Occupations		
Males: salesmen, printers, chauffeurs, merchants, students, painters, brokers, pressers, pedlers, bookkeepers, laborers, helper, awningmaker, silk manufacturer, iron worker, caretaker, janitor, advertising man, iceman, plumber, pharmacist, shipping clerk, floorer, butcher, knitter, neckwear operator, office worker, rabbi, physician, unmentioned (8)		
Females: housewives, students, nursemaid, hairdresser, school teacher, saleslady, nurse, dress operator, unmentioned (4)		
Trauma		
Mild	7	8.7
Severe	29	32.5
Illness		
Infection of the upper respiratory tract	6	7.5
Exposure to cold weather	2	2.4
"Arthritis"	1	1.2
Onset		
Insidious	25	32.0
Abrupt	53	68.0
Unknown	2	2.4
Backache		
1. Primary attacks (duration, 14.6 mo.)	53	66.3
2. Recurrent attacks (duration, 18.6 mo.)	27	33.7

An analysis of the symptomatology in these cases of sciatic scoliosis affords some interesting observations (table 2). The characteristic gait was a prominent feature. The greatest number of patients walked with the trunk stooped forward, flexion being either at the hip or at the sacrolumbar joints. Quite frequently the gait signs were combined in the same person, as the trunk forward (flexed) and guarded and an awkward gait.

Almost one third of the patients complained of generalized pain low in the back, while approximately one fourth indicated the sacro-iliac joints. Also, one fourth of the patients had pain over the buttock, which

TABLE 2.—*Symptomatology in Eighty Cases of Sciatic Scoliosis*

	Cases	Percentage
Gait		
Limp	13	16.0
Awkward	12	15.0
Guarded	6	7.5
Stooped forward	20	25.0
Unknown	29	31.5
Pain		
1. Location		
Sacro-iliac region	18	22.0
Lumbosacral region	1	1.2
Buttock	20	25.0
Lower part of back	29	31.5
Hip	10	12.0
Thigh	44	55.0
Leg	42	52.0
Foot	17	21.0
2. Sides		
Right	34	42.0
Left	41	51.0
Middle of back	5	7.0
Deformity of the back		
1. Standing position		
Tilt of trunk to the affected (painful) side*	25	33.0
Tilt of trunk to the well (painless) side†	48	63.0
Tilt of trunk alternating to the well, then affected side and (vice versa)	3	4.0
2. Prone position		
Disappearance of tilt	25	33.0
3. Physiologic curves		
A. Flatness or diminution of the normal curves		
a. Lumbar lordosis	34	51.0
b. Dorsal kyphosis	14	21.0
B. Complete reversal of the normal curves	11	16.0
C. Exaggeration of the normal curves		
a. Lumbar lordosis	4	5.9
b. Dorsal kyphosis	3	4.1
Mobility of the spine: 1. Restricted		
Flexion	63	78.0
Extension	52	65.0
Hyperextension	16	20.0
Lateral inclination	60	75.0
Muscle spasm	25	33.0
Tenderness		
Sacro-iliac region	41	51.0
Sciatic nerve		
Sacrosciatic notch	8	10.0
Thigh	19	23.0
Leg	14	17.0
Lumbosacral region	4	5.9
Gluteal region	11	16.0
Ilium	3	4.0
Lumbar muscle	7	10.5
None present	10	12.0
Straight leg raising		
1. Restricted,‡ (a) with pain in		
Left buttock	9	11.0
Left thigh	8	10.0
Left leg	3	4.0
Left sacro-iliac region	15	18.0
Left lumbosacral region	3	4.0
Right buttock	5	6.0
Right thigh	7	10.0
Right leg	2	2.5
Right sacro-iliac region	9	11.0
Right lumbosacral region	1	1.2
2. Unrestricted		
Left	12	15.0
Right	13	16.0
Neurologic signs		
1. Reflexes: absent or diminished on the affected side		
a. Patellar	4	5.9
b. Achilles	19	24.0
2. Sensory changes: hypalgesia		
a. Thigh	1	1.2
b. Leg	1	1.2
c. Foot	3	4.1
3. Atrophy		
Thigh	12	15.0
Leg	5	6.2
Buttock	3	4.1
Roentgen examination (41 cases) of pelvis and lumbar portion of spine		
1. Clinically affected side		
Haziness of the sacro-iliac joints (arthritic changes)	16	40.0
Arthritis of the lumbar portion of spine	9	22.0
Lumbosacral arthritis	2	5.0
Sacralization of the fifth lumbar vertebra	3	8.0
Negative	11	32.0

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* This was the side on which the pathologic process was present, viz., a derangement of that sacro-iliac joint.

† This was the side on which the pathologic process was absent.

‡ In many cases both the left and the right leg were restricted.

was usually most exquisite at the level of the sacrosciatic notch. Characteristic pain in the thigh (posterior aspect) and leg (lateral aspect) was present in over one half of the patients, and either one or both types of pain were associated with sensitivity low in the back or in the buttock.

In reviewing the deformity of the back with the patient in a standing position, it was interesting to find that almost two thirds of them tilted the trunk away from (dorsolumbar curve) the painful or affected side, whereas in one third the trunk was tilted to the painful side. In a small percentage (4 per cent) the tilt of the trunk alternated on successive examinations to the well and then to the afflicted side and vice versa. As brought out previously in criteria of structural versus functional scoliosis, with the patients in the prone position, one third of the deformities of the back disappeared prior to treatment, thus proving the functional status of the condition.

Associated with the tilt of the trunk were alterations in the normal physiologic curves. One half of the patients showed a flattening or diminution of the lumbar curves, and approximately one fifth revealed a flattening or absence of the dorsal kyphosis. Complete reversal of the normal curves, e. g., a lumbar kyphosis and a dorsal lordosis, was present in one sixth of the patients. In a relatively small percentage both of the normal curves were exaggerated.

The mobility of the spine was greatly affected. Approximately three fourths of all the spines were restricted in flexion, extension and lateral inclination. It was not unusual to find the various component motions associatively restricted. Also, muscle spasm could actually be observed in a third of the patients. On the foregoing basis, the awkward guarded gait which these patients presented was not an unexpected consequence of their disturbed muscle balance.

Sensitivity to pressure was found to be in the sacro-iliac joints in over half of the cases. Tenderness along the course of the sciatic nerve, from the sacrosciatic notch to the foot, was noted in about 60 per cent. The gluteal region was tender in one sixth of the cases. Tenderness prevailed in other areas but to a lesser extent.

Straight leg raising was restricted in the majority of the patients and was frequently associated with pain in one or the other sacro-iliac or lumbosacral joints or along the course of the sciatic nerve. Not infrequently, raising of the left and right legs was limited in the same person. Only in approximately one sixth of the patients was straight leg raising unrestricted.

The most striking neurologic sign was the absence of the achilles tendon reflex in one fourth of the patients on the affected (painful) side. Even after a result which was considered otherwise successful, it was not unusual to find that the achilles tendon reflex remained absent. Surprisingly few patients exhibited any hypalgesia, whereas atrophy of the thigh, leg and buttock was not infrequently found. This condition, no doubt, was of neurotrophic origin.

TABLE 3.—*Diagnosis of Sciatic Scoliosis Based on Etiology in Seventy-Seven Cases*

	Derangement of the Sacro-iliac Joint		Derangement of the Lumbosacral Joint	Periarthritis of the Lumbar Region of the Spine	Perineuritis of the Sciatic Nerve	Sciatica			
						Primary*		Secondary†	
	Left	Right				Left	Right	Left	Right
Left sciatic scoliosis Secondary to......	8 cases (10%)	8 cases (10%)	3 cases (4%)	1 case (1.2%)	1 case (1.2%)	3 cases (4%)	3 cases (4%)	8 cases (10%)	3 cases (4%)
Right sciatic scoliosis Secondary to......	14 cases (21%)	11 cases (16%)	3 cases (4%)	....	....	2 cases (2.5%)	1 case (1.2%)	3 cases (4%)	3 cases (4%)
Alternating (right and left) scoliosis Secondary to......	1 case (1.2%)	1 case (1.2%)	....	....	... ...	1 case (1.2%)			

* Due to a pathologic condition of the nerve, e. g., perineuritis of the sciatic nerve.
† Sciatica accompanying joint derangement and other extramural factors.

TABLE 4.—*Schematic Analysis*

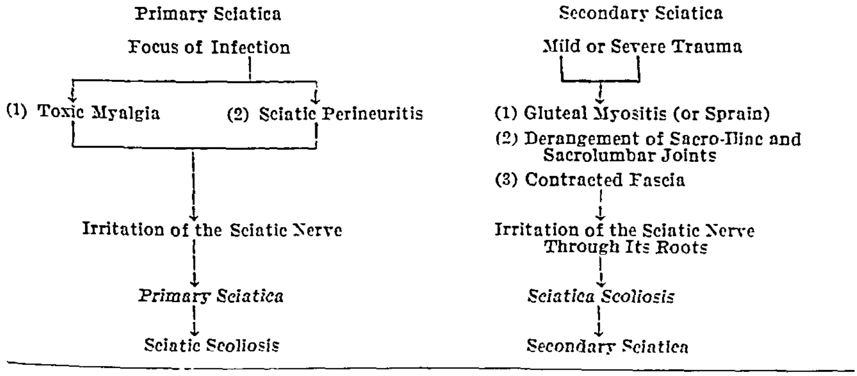

TABLE 5.—*Types of Treatment Used in Sixty-Four Cases*

1. Manipulation of the spine, stretching of involved limb under general anesthesia and application of plaster of paris spica bandage 2. Knight spinal brace	Traction followed by application of plaster spica	Application of plaster of paris spica under anesthesia; no stretching	Stretching followed by stripping of the gluteus medius muscle; application of plaster spica	1. Injection of sciatic nerve (procaine hydrochloride) 2. Stretching 3. Application of plaster spica	1. Caudal block (a) With stretching (b) Without stretching	Rest in bed
47 cases (73.5%)	2 cases (3.1%)	6 cases (9.2%)	3 cases (4.8%)	3 cases (4.8%)	1 case (1.5%)	2 cases (3.1%)

In reviewing the roentgenograms of the patients suffering from this condition, it was noted that a number did not show any pathologic process (one third). A larger number, however, revealed definite evidences of arthritic changes in the sacro-iliac joints and the lumbar region of the spine (two fifths).

The diagnosis of sciatic scoliosis was based on the exciting etiology. Sciatic scoliosis was practically as frequent on the left as on the right, and the infrequent alternating scoliosis was present in the remainder of the cases (3.8 per cent). Derangement of the joints low in the back was the most frequent exciting cause.

Primary sciatica followed inflammatory changes about the sciatic nerve proper, without involvement of the articulations low in the back. Either perineuritis or toxic myalgia, which was not uncommon after some infection of the upper respiratory tract, may have been the causative agent. In approximately one fifth of the eighty cases the sciatica was classified as primary. In these cases a typical diagnosis was stated as "left sciatic scoliosis, secondary to a right sciatica." Secondary sciatica, on the other hand, was found in those cases in which the exciting causes were derangement of the joints low in the back and gluteal myositides. In about one third of the eighty cases the sciatica was of this type. In this group a typical diagnosis was stated as "left sciatic scoliosis secondary to a derangement of the right sacro-iliac joint and a secondary right sciatica."

TREATMENT

The treatment, which was dependent on the severity of the condition, resolved itself in a uniform set of procedures. In the cases of mild involvement, those in which the sciatic pain was only moderate or mild, the treatment consisted of rest in bed, caudal blocks, injections into the sciatic nerve (at the sacrosciatic notch), unbalanced traction or the application of plaster of paris spica jackets. In the cases of severe involvement, in the majority of which hospitalization was necessary, the technic as followed by Kleinberg[1] was used. The patient was placed on a Hawley table and completely anesthetized; the spine was then manipulated by passive flexion, lateral inclination and hyperextension. The involved extremity, with the knee extended to 180 degrees was flexed at the hip so that the foot was within 15 to 20 inches (38 to 50.8 cm.) of the patient's face, the distance being dependent on the status of the elasticity of the tissues. The involved as well as the uninvolved limbs were brought into hyperextension, thus reforming the physiologic dorsal and lumbar curves. Plaster of paris was applied to the torso, and after it set the involved limb was brought anterior to 180 degrees at the hip. The plaster was then continued to include the toes. The patient was left in this plaster bandage for three weeks, after which time a Knight spinal brace was applied, and physical therapy in the form of baking and massage was instituted. After six weeks the patient was allowed out of bed and gradually permitted to walk.

Because of tenseness of the gluteus medius muscle and the adjacent fascia, in addition to the stretching procedure as described, the muscle was stripped from its iliac attachments in three cases.

The results were most gratifying after the stretching procedure. In only two instances was a second stretching necessary in order to obtain a satisfactory result. The follow-up period in these cases varied from a few months to five years.

COMMENT

This paper is limited to a discussion of pain low in the back due to derangements of the sacro-iliac and lumbosacral joints and to myositides of the gluteal muscles and primary sciatica. Such lesions as tumors of the spinal cord and involvement of the urogenital tract were not considered, although it is appreciated that they can produce symptoms which may simulate those of sciatic scoliosis.

SUMMARY

Sciatic scoliosis is a clinical syndrome characterized by: lateral curvature of the spine, not infrequent pains low in the back, an awkward guarded gait with a limp, restricted mobility of the spine, tenderness of the joints low in the back and along the course of the sciatic nerve, restricted straight leg raising, not infrequent absence of the achilles tendon reflex on the affected side and relatively few roentgenographic changes.

Eighty patients were studied, sixty-four of whom were treated. The condition in three fourths of these was of the severe type; therefore the stretching procedure and plaster spica bandages were used.

The results were uniformly very satisfactory.

MULTIPLE PERIPHERAL ANEURYSMS ASSOCIATED WITH NONSYPHILITIC DEGENERATION OF THE TUNICA MEDIA

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While multiple small aneurysms of the cerebral and of the pulmonary vessels have been discovered at necropsy, and multiple aneurysms of various of the individual intra-abdominal arterial trunks have been found at operation and at postmortem examination, but relatively few cases of multiple peripheral aneurysms have been reported. Among these may be mentioned the cases of Monro,[1] Kolodny,[2] Aloi,[3] Wilbur,[4] Lemonnier and Bouysset[5] and Leriche and Jung.[6] However, only in the case reported by Aloi, in which aneurysms developed in both popliteal spaces, were all the aneurysms treated surgically.

We wish, therefore, to present a clinical and a pathologic study of a remarkable case, one in which there were at least five major peripheral aneurysms involving the left femoral, right femoral, right popliteal, right subclavian and left axillary arteries; while the aorta and its primary branches were also the seat of the disease which we believe was responsible for the development of the peripheral aneurysms, they were free from any dilatation. The case was further remarkable for the fact that in the process of the surgical treatment of the aneurysms all the major branches of the aorta leading to the head and extremities, except the left carotid artery, were successively ligated without the

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1. Monro, D., in Erichsen, J. E.: Observations on Aneurysm, London, Sydenham Society, 1844, pp. 130-132.

2. Kolodny, A.: Multiple Aneurysms of Large Vessels: Report of a Case, J. A. M. A. **86**:397 (Feb. 6) 1926.

3. Aloi, V.: Un caso di aneurisma multiplo, Ann. ital. di chir. **6**:1121, 1927.

4. Wilbur, D. L.: Multiple Aneurysms of the Arteries of the Right Arm Associated with Arteriovenous Fistula and Arterial Embolism: Report of Case, Am. J. M. Sc. **180**:221, 1930.

5. Lemonnier and Bouysset, C.: Anévrysmes multiples des membres inférieurs dont un avec rupture, Lyon chir. **30**:287, 1933.

6. Leriche, R., and Jung, A.: Neuf anévrysmes latents de la fémorale, de la poplitée et de ses branches. Gangrène de l'avant-pied avec crises vaso-constrictives, Lyon chir. **31**:182, 1934.

production of circulatory deficiency in the brain or in any of the extremities and without any clinical evidence of cardiac embarrassment.

REPORT OF A CASE

History.—A 52 year old Italian-Swiss musician was first admitted to the New York Hospital on Oct. 14, 1932, complaining of "throbbing lumps" on his body. His family history was unimportant, all the members having lived to old age. His past history was significant, however, in several features: He had had diphtheria as a child, with the development of a cervical abscess, which required incision. He also underwent an operation for hernia as a child, which was followed by a recurrence at the age of 20. At 30 an umbilical hernia developed, and this and the recurrent inguinal hernia were successfully repaired the following year. In 1913, at the age of 33, he suffered from "blood poisoning" after stepping on a nail. The local abscess in his foot was incised and drained for two months. In 1921 acute appendicitis developed with peritonitis, for which he was operated on; he remained in the hospital for two months, during which time the wound drained.

There was no history of chancre or of any rash or other type of lesion which might be interpreted as secondary or tertiary syphilis. All Wassermann tests had been negative. In 1931 the patient had some ulcers on his left leg, which healed after the application of an elastic bandage.

The first symptoms referable to the illness under discussion occurred in January 1931, when the patient first noticed a small pulsating lump in the right popliteal space about 4 by 4 cm. in size. This remained about the same size and was painless until January 1932, when it became larger and painful. It then became intermittently painful, causing shooting pains up to the hip and down the back of the leg, with some numbness of the toes and sole of the right foot. In September 1931, pain developed in the right shoulder and arm with numbness of the ring and little fingers of the right hand, and subsequently the patient noted a small, throbbing, painful mass in the right supraclavicular region.

In June 1932 he noted a similar but smaller pulsating mass beneath the outer end of the left clavicle, which caused local pain and was associated with numbness and pain radiating down the left arm to the fingers. About the same time he discovered a small pulsating tumor, 2 by 3 cm. in size, in the left groin, which increased rapidly in size until, at the time of his first admission to the New York Hospital, it was 10 cm. in diameter and caused pain locally.

Finally, in September 1932 a fifth pulsating mass was recognized in the right groin, which was about 6 by 6 cm. in size and was also painful, and which, like all the other masses, caused more pain when the patient was up and about.

Examinations.—On the patient's first admission to the hospital physical examination revealed a fairly well nourished man of about the stated age who had difficulty in walking. The head and neck were normal, except for the presence of a scar about 6 cm. in length on the right side of the neck, evidently the site of incision of the cervical abscess. The chest was well developed, its expansion was normal and there were no evident bony deformities.

At the base of the neck on the right, occupying the mesial portion of the supraclavicular fossa, was a pulsating mass, 6 by 6 cm. in size, over which a systolic thrill could be felt. Auscultation of the mass revealed a bruit synchronous with the cardiac systole. Pressure over this swelling obliterated the right radial pulse.

The heart was apparently normal in size, rhythm and rate. A soft systolic murmur could be heard over the base of the heart up to the neck, which was thought to be transmitted from the aneurysm. The lungs were clear throughout, and there was no evidence of widening of the area of mediastinal dulness.

The abdomen was slightly protuberant, and its wall was soft and relaxed. A large ventral hernia was present in the right lower quadrant, and here the abdominal wall was thin and contained a large defect. A transverse linear scar 16 cm. in length was evident at the level of the umbilicus. The liver and spleen were not felt, and no masses, tenderness or bruit could be made out in the abdomen. The genitalia were normal, and rectal examination revealed nothing abnormal.

In the left groin and extending downward to the apex of Scarpa's triangle was a swelling, 12 by 12 cm., with an expansile pulsation. A soft systolic bruit was audible over this, and firm pressure on it obliterated the pulsation in the left dorsalis pedis artery.

A smaller pulsating mass, 6 by 8 cm., was evident in the right groin below Poupart's ligament, and over this also a systolic bruit could be heard. A fifth and similar mass, 8 by 12 cm. in size, was to be seen in the right popliteal space. Pressure over this caused the pulsation in the right dorsalis pedis artery to disappear.

Neurologic examination revealed paresthesia over the distribution of the antebrachial cutaneous nerves of the forearms and numbness in the ulnar distribution in the hands. The left leg was normal, but there was definite paresthesia over the lateral aspect of the right foot extending out on the fourth and fifth toes. An area of numbness was present over the arch of the right foot.

The laboratory findings at the time of this admission were unremarkable. The Wassermann and Klein tests of both the patient and his wife were negative. The spinal fluid was negative, and the colloidal gold curve was normal. A blood culture was also negative.

Course.—After the patient's discharge from the hospital on December 14, the aneurysms increased in size and caused considerable pain. The paralysis of the right ulnar nerve became more marked, and absolute numbness developed over the anterolateral portion of the right leg, with marked hyperesthesia on the plantar surface of the foot. Wasting of the muscles of all extremities became so marked that the patient was "bedridden," and his right hand became so paralyzed as to be quite useless.

While all the aneurysms increased in size, that in the left femoral region grew most rapidly, until in the early part of February 1935 it had reached the size of a child's head. The skin over it became discolored and necrotic, and blood began to ooze from it. The patient was readmitted to the hospital on February 20.

At this time the findings were essentially as outlined, all the aneurysms having increased in size. The radial pulses were of normal volume, but the pulsations in both dorsalis pedis arteries, although present, were diminished as compared to their size on the patient's previous admission. The blood pressure in the right arm was 110 systolic and 94 diastolic; that in the left arm was 122 systolic and 92 diastolic.

Operations.—On February 25, with the patient under general anesthesia, a left rectus incision was made, and the left common iliac artery was exposed and ligated by means of linen tape. After operation the left leg was closely watched; at no time, however, did its color change. The skin temperature remained within normal limits, and there was no evidence of a deficiency in the circulation. The blood pressure in the left arm at this time was 130 systolic and 100 diastolic. Ten days later it had fallen somewhat, being 95 systolic and 80 diastolic in the right arm and 110 systolic and 85 diastolic in the left arm. The left leg was placed in the Pavaex machine early in the postoperative period. The abdominal wound healed well, and there continued to be no change in the left leg. The aneurysm ceased to pulsate immediately after ligation of the artery and showed no signs of activity subsequently. It decreased somewhat in size, but three consecutive aspirations were performed through healthy tissue in an unsuccessful attempt to prevent necrosis of the skin over its anterior aspect. The patient's course continued favorably, but because the aspirations continued to yield fresh blood, on April 3, with procaine hydrochloride for local anesthetization a longitudinal incision was made on the medial aspect of the left thigh, the femoral artery was located and ligated, and a piece about 2 cm. in length was excised. The skin over the peak of the aneurysm sloughed, however, and despite proximal and distal ligation of the artery, blood continued to ooze from the sloughed area. Therefore, on April 6, with the patient under general anesthesia, a longitudinal incision was made over the aneurysm, the entire sac was evacuated of its clots, the femoral artery was doubly ligated within the sac and the cavity was packed. The packs were removed on the fourth postoperative day, and the wound was treated with saline solution. Under this treatment it gradually healed with clean and healthy granulations.

Fig. 1.—Aneurysm in the left femoral region just before ligation of the left common iliac artery, showing necrosis of the skin over the aneurysm.

During this period the patient's greatest discomfort arose from the aneurysm in the right subclavian region, which was increasing in size. He was losing the function of his arm, and examination on June 15 revealed marked atrophy of the entire right arm, most noticeable in the right hand where the interosseus muscles were almost completely atrophied. He had an early clawhand, and neurologic examination revealed almost complete palsy of the median and ulnar nerves. While this was developing he had a great deal of pain in the arm and hand, which gave way to numbness, especially in the hand. On June 14, with the patient under general anesthesia, an incision was made over the medial portion of the clavicle on the right side, and the right innominate artery was tied off with linen tape, just proximal to its bifurcation into the carotid and subclavian arteries. Subsequent to this procedure the anuerysm ceased to pulsate, and no definite pulsation could be made out in either the radial or the temporal arteries. The blood pressure in the left arm after this procedure was 120 systolic and 80 diastolic.

It was remarkable to see the return of function and of feeling in the right hand and arm. At this time the patient could approximate the thumb and little finger, could extend and abduct the fingers moderately and could distinguish between blunt and sharp objects.

Course.—June 18: Complete physical examination on this date revealed the patient's general condition to be slightly altered from that at the time of admission. There was no demonstrable change in the heart, either as to size or sounds. The lungs were clear. The wound in the left femoral region was healed except for an area of about 4 cm. in length, 2 cm. in width and 3 cm. in depth, which was covered with clean granulations. The aneurysm in the left axilla did not seem to be causing any increase in symptoms and had not changed appreciably in size. The aneurysm in the right subclavian region yielded no pulsation. The operative wound was clean and healing well. The aneurysm in the right femoral region was not causing any symptoms but showed a slight increase in size. The aneurysm in the right popliteal space, which was by far the largest of all, did not appear to be causing any further symptoms, but it too was thought to be slightly increased in size.

The oscillometric readings (in units) were as follows:

Left Arm—B. P. 124/80		Right Arm—B. P. not obtained	
Upper part of arm	5.5	Upper part of arm	0.5
Forearm	4.0	Forearm	0.3
Left Leg		Right Leg	
Thigh	0	Thigh	5.0
Calf	0	Calf	3.5
Ankle	0	Ankle	3.5

The skin temperatures (C.) recorded at this time follow:

	Right	Left
Forehead	31.5	31.0
Cheek	30.5	30.5
Neck	34.0	33.0
Shoulder	32.0	33.0
Arm	32.0	31.0
Forearm	33.0	33.0
Dorsum of hand	34.0	34.0
Palm of hand	34.0	34.0
Chest	33.0	33.0
Abdomen	33.0	33.0
Thigh	33.0	32.5
Calf	32.0	30.5
Dorsum of foot	32.0	29.0
Plantar surface of foot	32.0	29.0

June 28: During the preceding week the patient's course was smooth and without complications. Examination on June 28 revealed the remainder of the aneurysms as previously stated, without change. The one in the right subclavian region still revealed no pulsation and had diminished in size. The wound had healed well, and the stitches had been removed. There was no radial pulsation felt in the right arm, and no temporal pulse could be palpated on the right side. The patient's greatest difficulty had been in the left knee, which still remained in a flexed position and was tender. Physical therapy afforded some relief.

The following oscillometric readings (in units) were obtained at this time:

	Right—B. P. 0/0	Left—B. P. 104/78
Upper part of arm	0.8	6.0
Forearm	0.5	6.0
Thigh	5.0	0.5
Calf	3.5	0
Ankle	3.5	0

July 5: During the preceding week there was one new development. Some pus discharged from the incision in the right clavicular region where the innominate artery was tied off. The wound was opened in one area, and a considerable quantity of pus was evacuated. The patient's general condition remained good. There were no pulsations felt in the right wrist or in the temporal region. The contracture of the left knee was responding favorably to physical therapy, the pain being less and the motion increased.

The following oscillometric readings (in units) were obtained:

	Right—B. P. 0/0	Left—B. P. 104/78
Upper part of arm	0.8	6.0
Forearm	0.5	6.0
Thigh	5.0	0.5
Calf	3.5	0
Ankle	3.5	0

July 12: During the preceding week there was little change in the patient's condition. Neither the right radial nor the temporal pulse could be felt. The aneurysm in the right subclavian region remained dead. The wound in the right clavicular region, which had been discharging pus, owing to through and through irrigations with saline solution had granulated and was not discharging any longer. The wound in the left femoral region was almost entirely healed. The patient had been sitting up on the edge of the bed with no ill effects. When he sat up it was seen that there was a slight purplish discoloration in the left leg and the right arm.

July 19: The wound in the right clavicular region, previously alluded to, was completely healed. There was no obvious change in any of the aneurysms. The one in the right subclavian region remained dead, with no evidence of either temporal or radial pulsation on the right side. The patient had been sitting on the edge of the bed. Motion in the left knee was gradually returning, and the contracture was reduced about 60 per cent.

July 26: During the preceding week there was little change in the patient's condition. The aneurysms remained as previously stated. The wound in the left groin and the wound in the right clavicular region were practically healed. Pulsations in the right wrist and temporal region were not felt. The patient sat at the edge of the bed every day, and while he was in the upright position cyanosis of the left leg and of the right arm was visible. General physical examination revealed nothing new.

The following oscillometric readings (in units) were obtained:

	Right—B. P. 0/0	Left—B. P. 118/82
Upper part of arm	0.5	4.5
Forearm	0.5	4.0
Thigh	3.5	0
Calf	2.5	0
Ankle	2.5	0

August 28: In the interval since July 26 the aneurysms remained essentially the same. The wound in the left inguinal region was well healed. During the first two weeks the patient's condition was good. On August 15 he had a temperature of 39 C. (102.2 F.), which persisted for three days. The area around the wound in the chest, which by this time was well healed, became indurated. A clamp was inserted, and some changed blood was evacuated. The fever persisted for three days and then subsided after adequate drainage was established. The wound cavity was irrigated thoroughly with saline solution. On August 18 a massive hemorrhage from this wound occurred, and the patient lost at least a liter of blood. The hemorrhage was well controlled by packs, and the patient's condition improved and at this time was very good. No pulsations were felt in the right wrist or in the temporal region. There was definite cyanosis of the left leg and right arm when the patient sat up.

The following oscillometric readings (in units) were obtained:

	Right—B. P. 0/0	Left—B. P. 120/80
Upper part of arm	0.1	5
Forearm	0.1	4
Thigh	3.5	0
Calf	2.5	0
Ankle	2.5	0

September 16: Since August 28 there had been little change in the patient's general condition. His blood count returned to normal, and he stated that he was quite comfortable. There was a definite progression of the aneurysm in the right popliteal region, which had increased both in length and in diameter. It measured 20 cm. in length, and the thigh at the center of this aneurysm measured 50.5 cm., as compared to 39 cm. for the left thigh at a similar position. The aneurysm in the left subclavian region had also grown considerably. The patient began to notice increased numbness in the left index finger and the same condition, but to a less extent, in the left middle finger. The wound in the left inguinal region was now well healed. There was only a slight degree of drainage. The wound in the right subclavian region had healed remarkably well. There was no purulent drainage at this time. General physical examination revealed nothing new. No pulsations were felt in the right wrist or in the temporal region. When the patient sat up in bed, cyanosis of the left leg and arm was visible. He felt that he was gaining some use of his left leg.

Neurologic examination revealed nothing new except for slight diminution of sensation over the left index finger and, to a lesser degree, over the left middle finger.

The following oscillometric readings (in units) were obtained:

	Right—B. P. 0/0	Left—B. P. 120/80
Upper part of arm	0	2.5
Forearm	0	2.0
Thigh	10.0 (over aneurysm)	Trace
Calf	3.0	0.2
Ankle	1.5	0.2

The skin temperatures (C.) at this time were:

	Right	Left
Forehead	33.5	33.5
Cheek	32.5	33.0
Neck	33.5	34.5
Shoulder	33.5	33.5
Arm	33.0	33.5
Forearm	32.5	32.5
Dorsum of hand	31.5	32.5
Palm of hand	31.5	32.5
Chest	32.5	33.5
Abdomen	31.5	31.5
Thigh	30.9	31.5
Calf	30.0	30.5
Dorsum of foot	28.5	29.0
Plantar surface of foot	28.0	28.5

September 18: A right rectus incision was made, and the right common iliac artery was ligated with a catgut ribbon ½ inch (1.3 cm.) in width. Immediately after the ligation all pulsations ceased in the aneurysms in the inguinal and popliteal regions, and the extremity became cooler. There was no venous distention. The pulses of the popliteal, the posterior tibial and the dorsalis pedis arteries could not be felt. One hour after the patient was returned to the ward, oscillometric readings showed that there were no pulsations in the right leg as measured over the thigh, calf and ankle. The oscillometric reading preoperatively over the aneurysm was 10 units; postoperatively, it was 0 units. The extremity regained heat rapidly, so that one hour after operation the skin temperatures (C.) were as follows:

	Right	Left
Dorsum of foot	30	30.0
Plantar surface of foot	30	29.5
Calf	31	32.0
Thigh	32	33.0

Five hours after operation the oscillometric readings were 0, the extremities were warm, and no pulses could be felt in either foot.

September 19: Up to this time the patient's course had been uneventful. The right leg was warm; there were no pulsations in either aneurysm. The pulses of the popliteal, posterior tibial and dorsalis pedis arteries were still absent. Oscillometric readings were 0 over the thigh, calf and ankle.

The skin temperatures (C.) were as follows:

	Right	Left
Dorsum of foot	30.5	30.5
Plantar surface	29.5	30.5
Thigh	31.5	32.5
Calf	31.5	31.5

September 24: Since September 19 the patient's course had been satisfactory. The wound healed per primam, and all the skin sutures were removed on the sixth postoperative day. The aneurysm in the popliteal space had no pulsation. There was slight pulsation in the aneurysm in the right femoral region. The pulses of the popliteal, posterior tibial and dorsalis pedis arteries were still absent. Oscillometric readings (in units) over the calf, thigh and ankle were still 0.

The skin temperatures (C.) were as follows:

	Right	Left
Dorsum of foot	29.8	29.5
Plantar surface	29.0	29.5
Calf	31.0	31.0
Thigh	32.0	32.0

There was still slight drainage from the left groin. The wound cavity in the right subclavian region was now clean, and there was no drainage. The aneurysm in the left subclavian region had not changed noticeably since the last observation, and the patient's neurologic condition was unchanged.

October 8: The patient's course had been uneventful since the last report. The lower right rectus wound was healing. There was a small pus pocket at the side of the lower two through and through silver sutures. This was opened adequately and was irrigated with saline solution. The silver wires were still in place. There was definite, but slight, pulsation in the aneurysm in the right femoral region, which had also decreased in size. The preoperative measurement of the right thigh in the center of this aneurysm had been 50.5 cm., but now was 41.5 cm. The pulses of the popliteal, posterior tibial and dorsalis pedis arteries were absent bilaterally. The wound in the left groin was still draining slightly. The wound in the right subclavian region was fairly well healed. There were no pulsations of the aneurysm in the right subclavian region, and its size was essentially the same. The aneurysm in the left subclavian region had increased slightly in size. General neurologic examination revealed the persistence of the paralysis of the right ulnar nerve, both motor and sensory components being involved, as before. There was persistence of the absence of sensation over the anterior surface of the lower part of the left leg and dorsum of the foot, with hyperesthesia over the plantar surface of the left foot. Sensation of the right leg and foot was intact. There was an area of hypesthesia over the flexor surface of the left index finger, and the same condition persisted to a lesser extent over the distal portion of the flexor surface of the left thumb and the second finger.

The following oscillometric readings (in units) were obtained:

	Right	Left
Upper part of arm	Trace	4.2
Forearm	Trace	3.5
Thigh	0	0
Calf	0	0
Ankle	0	0
B. P., arm	0/0	120/80
B. P., calf	0/0	0/0

The readings for the skin temperature were essentially the same as those obtained on September 16, before ligation of the right common iliac artery.

October 16: Since October 8 the patient's course had been satisfactory. The lower right rectus wound was healing well. The infection at the site of the stay sutures, which were removed on the twenty-first postoperative day, had now practically subsided. There was definite pulsation in the aneurysm in the right femoral region, which had greatly decreased in size. The aneurysm in the popliteal space showed no pulsation, and there had been no change in its diameter in the past few weeks. The pulses of the popliteal, posterior tibial and dorsalis pedis arteries were still absent bilaterally. There was still slight drainage from the wound in the left groin and in the right subclavian region. The aneurysm in the right subclavian region was free of pulsation and had definitely decreased in size. The one in the left subclavian region had increased in size. Atrophy was present in the muscles innervated by the left median nerve. Loss of sensation of the flexor surfaces of the left thumb, index and middle fingers had increased, and the palsy of the right ulnar nerve persisted.

The oscillometric readings (in units) were as follows:

	Right—B. P. 0/0	Left—B. P. 96/64
Upper part of arm	0	0.5
Forearm	0	1.0
Thigh	0	0
Calf	0	0
Ankle	0	0

The oscillometric readings and neurologic examination showed definitely increasing involvement of both the vascular and the nerve elements of the left arm. During the past eight days there was marked decrease in the oscillometric readings obtained on the left arm.

November 18: Since October 16 the patient's course had progressed satisfactorily. The lower right rectus wound had a persistent draining sinus. On November 17 a black silk suture was removed, and it was felt that healing should take place. The wounds in the left groin and right subclavian region had completely healed by this time, and the aneurysm in the right subclavian region was definitely smaller and showed no pulsation. The aneurysm in the left axilla had increased considerably in size, and the pulsation had increased. The patient had considerable pain in the left shoulder and in the left arm. The size and pulsation of the aneurysm in the right femoral region remained constant. The aneurysm in the popliteal space showed no pulsation, and the leg here measured 41.5 cm. in circumference. General physical examination showed no abnormalities in the heart and lungs.

Neurologic examination revealed an area of hyperesthesia over the left index finger on its flexor surface. The left hand could not be fully closed, and there was atrophy of the muscles supplied by the median nerve. Subjective numbness was present in the left index finger. Sensation in the right hand was improved. The atrophy in the muscles supplied by the ulnar nerve persisted, but the hypesthesia of the fourth and fifth fingers was less marked. The reflexes of the left arm were physiologic; those of the right were absent. Examination of the left leg revealed marked improvement, but the hyperesthesia of the plantar surface of the left foot persisted. The patient at this time could discriminate heat, pinprick, touch, etc., on the ventral surface of the lower part of the left leg and the dorsum of the foot, and the leg could be almost completely straightened. Sensation in the right leg was normal, as were reflexes in the lower extremities.

The following oscillometric readings (in units) were obtained:

	Right—B. P. 0/0	Left—124/80
Upper part of arm	0	1.5
Forearm	0	1.5
Thigh	0	0
Calf	0	0
Ankle	0	0

The skin temperatures (C.) were as follows:

	Right	Left
Upper part of arm	31.0	31.0
Forearm	32.0	31.0
Palm of hand	32.0	32.5
Thigh	32.5	32.0
Calf	32.5	31.5
Ankle	32.5	32.0
Dorsum of foot	33.0	32.0
Plantar surface of foot	32.5	31.5

December 10: The patient's general condition remained excellent. The infection at the site of the right rectus wound subsided, and the wound was completely healed.

With the patient under ethylene anesthesia, ligation of the left subclavian artery was performed. An incision 6 cm. long and parallel to and above the level of the clavicle was made, and the skin and platysma were divided. By means of careful dissection, the clavicle was isolated, and a section of it was removed. The distal fragment was then immobilized inferiorly. The subclavian artery was readily identified, as was the aneurysm. Blunt and sharp dissection were employed, the subclavian artery was ligated with a broad tape and the wound was closed. Throughout and after the procedure the patient's condition remained satisfactory. Directly after the operation the left extremity felt warm. The radial pulse was no longer palpable.

The oscillometric readings on the left arm were all 0.

The skin temperatures (C.) were as follows:

	Right	Left
Directly after operation:		
Forearm		30.0
Palm of hand		31.0
Dorsal surface of hand		31.0
Four hours after operation:		
Forearm		30.0
Hand		32.0
Eight hours after operation:		
Forearm	30.0	31.5
Hand	30.5	31.0
Twenty-four hours after operation:		
Forearm	30.5	31.5
Hand	31.5	32.5

December 26: The patient's postoperative course was uneventful, and the wound healed per primam. The aneurysm in the left subclavian region ceased to pulsate, and its size decreased rapidly. There was no objective change in the circulation of the hand and arm. All other wounds were now well healed. The aneurysm in the right popliteal space was unchanged. It was completely free from pulsation and constant in size. However, the aneurysm in the right femoral region had increased markedly in size and pulsated vigorously. A pulsating mass also appeared above Poupart's ligament, and the patient complained of pain in the region of the bladder and urgency in urination. He also experienced frequent attacks of shooting pain in the right lower abdominal quadrant and the right groin.

General examination revealed that there were no peripheral pulses. Neurologic examination was unchanged. The right ulnar palsy persisted, and there was an early median palsy of the left hand.

Oscillometric readings on all extremities were 0. The skin temperature remained unchanged since the last examination.

Jan. 1, 1936: The aneurysm in the right lower abdominal quadrant increased rapidly in size and formed an extremely large mass, filling almost the entire quadrant. On December 29 it doubled in size, and at 7 a. m., January 1, it ruptured into the abdominal cavity, causing the patient's death.

Autopsy.—Autopsy was performed four hours after death. The body was that of a well developed, well nourished white man 52 years of age and weighing 75 Kg. There was a marked pallor of the skin and mucous membrane. There were healed surgical incisions in both infraclavicular regions. On the right there had been a resection of the first rib. There were three surgical incisions in the lower abdominal region, all of which were well healed. In addition there was a well healed incision in the left femoral region. There were large firm masses in the left and right infraclavicular, right inguinal, right femoral and right popliteal regions. The extremities showed advanced muscular atrophy.

When the peritoneal cavity was opened, 100 cc. of thin bloody fluid was found. There was a large firm mass just above Poupart's ligament on the right. The wall of this mass was made up of thin friable tissue containing a large clot of fresh blood. There was a similar large clot in the region of the splenic flexure of the colon.

The organs, other than the circulatory system, showed no gross pathologic change. Therefore, only the heart and arterial system will be described in detail.

The heart weighed 320 Gm. It showed no gross pathologic change other than that the coronary arteries were thin walled and dilated. The dilatation took place within a few millimeters of their origin. These arteries showed only a slight degree of sclerosis of the intima.

The aorta was not dilated. Its wall was of the usual thickness, and arteriosclerosis of the intima as characterized by plaque formation was present only to a slight degree at the root of the aorta and in the region of its bifurcation. The innominate artery was not dilated. It was ligated with white linen tape just proximal to the origin of the right common carotid artery. Beneath the ligature the lumen was completely occluded, and the wall of the vessel was replaced by fibrous connective tissue. The right subclavian artery beyond the ligature was thin walled but not dilated. Three centimeters from its origin there was a large fusiform dilatation of the vessel, which on section was found to be made up of greatly thinned arterial wall containing a firm, laminated blood clot. The aneurysm was really made up of two continuous sacs, measuring 6.5 and 2 cm. in diameter, respectively. Firmly adherent to the posterior wall of the aneurysm and compressed by it were the major cords of the right brachial plexus. The axillary artery beyond the aneurysm was thin walled but not dilated.

The right and left common carotid arteries showed no gross pathologic change. The left subclavian artery showed a slight degree of arteriosclerosis. Seven centimeters from the aortic arch the vessel was ligated with white linen tape. The lumen of the vessel was just occluded by the ligature, beyond which there was a fusiform dilatation of the artery, measuring 5 by 4 cm. in diameter. On section, the aneurysm was found to be made up of a greatly thinned arterial wall containing a firm, laminated blood clot. The major cords of the left brachial plexus and the great nerves to the arm were compressed by the aneurysm.

As the celiac axis and the right renal and the left renal arteries left the aorta they became extremely thin walled and dilated. They measured 1.5, 1 and 1 cm. in diameter, respectively. These vessels showed a more advanced arteriosclerotic change than the vessels just described. However, the greatest pathologic change was in the media, which appeared irregularly thin and was waxy gray. The splenic artery showed a mild degree of arteriosclerosis and tortuosity. It showed a medial change similar to that described. The left common and left external iliac arteries showed advanced arteriosclerotic change. The left external iliac artery had been ligated with white linen tape just proximal to its origin. The lumen of the vessel was occluded both distal and proximal to the ligature by a firm laminated clot, which showed some early organization.

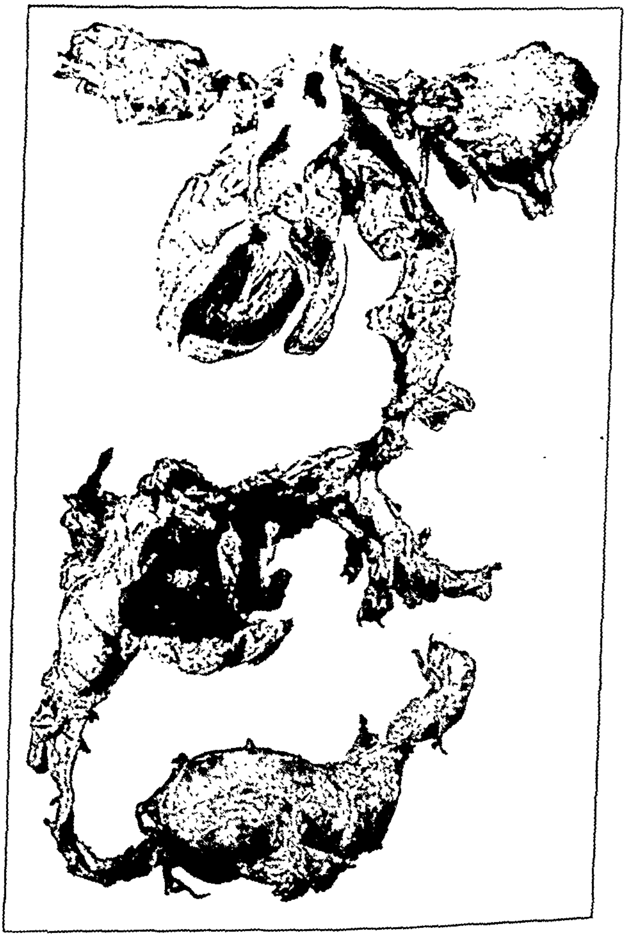

Fig. 2.—Photograph of autopsy material showing the major arteries and the position and size of the aneurysm.

There was a moderate degree of arteriosclerosis of the right external iliac artery. The vessel contained a fusiform dilatation, beginning 3 cm. from its origin. This aneurysm was 15 cm. in length and varied from 10 to 5 cm. in diameter. It extended beneath Poupart's ligament and was compressed by it. The largest portion of the aneurysm was directed anteriorly. Here the wall was made up partially of thinned vessel and partially of peritoneum and fibrous connective tissue. There was a small portion of the aneurysm directed posteriorly the wall of which was made up partially of the wall of the vessel and partially of fascia covering the iliolumbar muscle. The aneurysm had ruptured posteriorly along the sheath of the iliolumbar muscle. On section, the lower part of the aneurysm was found filled with a firm, laminated blood clot. The upper portion contained a moderately fresh blood clot. The linen ligature used in an attempt to occlude the aneurysm was present surrounding the aneurysm at the point of rupture. The right femoral artery was thin walled and showed advanced dilatation. There were many transverse bars of calcium in the media typical of the Moenckeberg type of arteriosclerosis. There were two large fusiform aneurysms in the popliteal space. The largest of these was 14 cm. in length and 7 cm. in its greatest diameter. The smallest was 7 cm. in length and 2.5 cm. in its greatest diameter. They both were made up of an extremely thin vessel wall and contained a laminated blood clot.

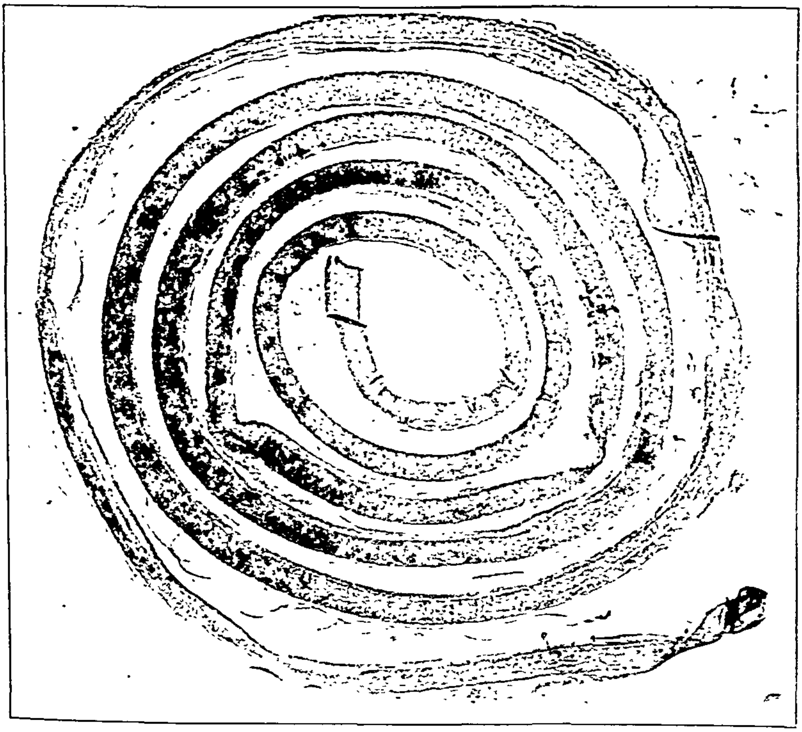

Fig. 3.—Section of the descending aorta, showing the method of cutting so that the entire aorta can be seen in one section. Two advanced lesions are to be seen. Weigert's elastic tissue stain; × 8.

The majority of the vessels were examined microscopically throughout their length by cutting rolled sections, as shown in figure 3. The sections were all stained with hematoxylin and eosin and with Weigert's elastic tissue stain. Special sections were stained for fat with sudan III. Masson's stain was used to differentiate muscle and connective tissue. The chromotropic substance was specially demonstrated by the use of thionine and polychrome methylene blue. Calcium was stained by the use of the von Kossa silver nitrate method. Brown's bacterial stain

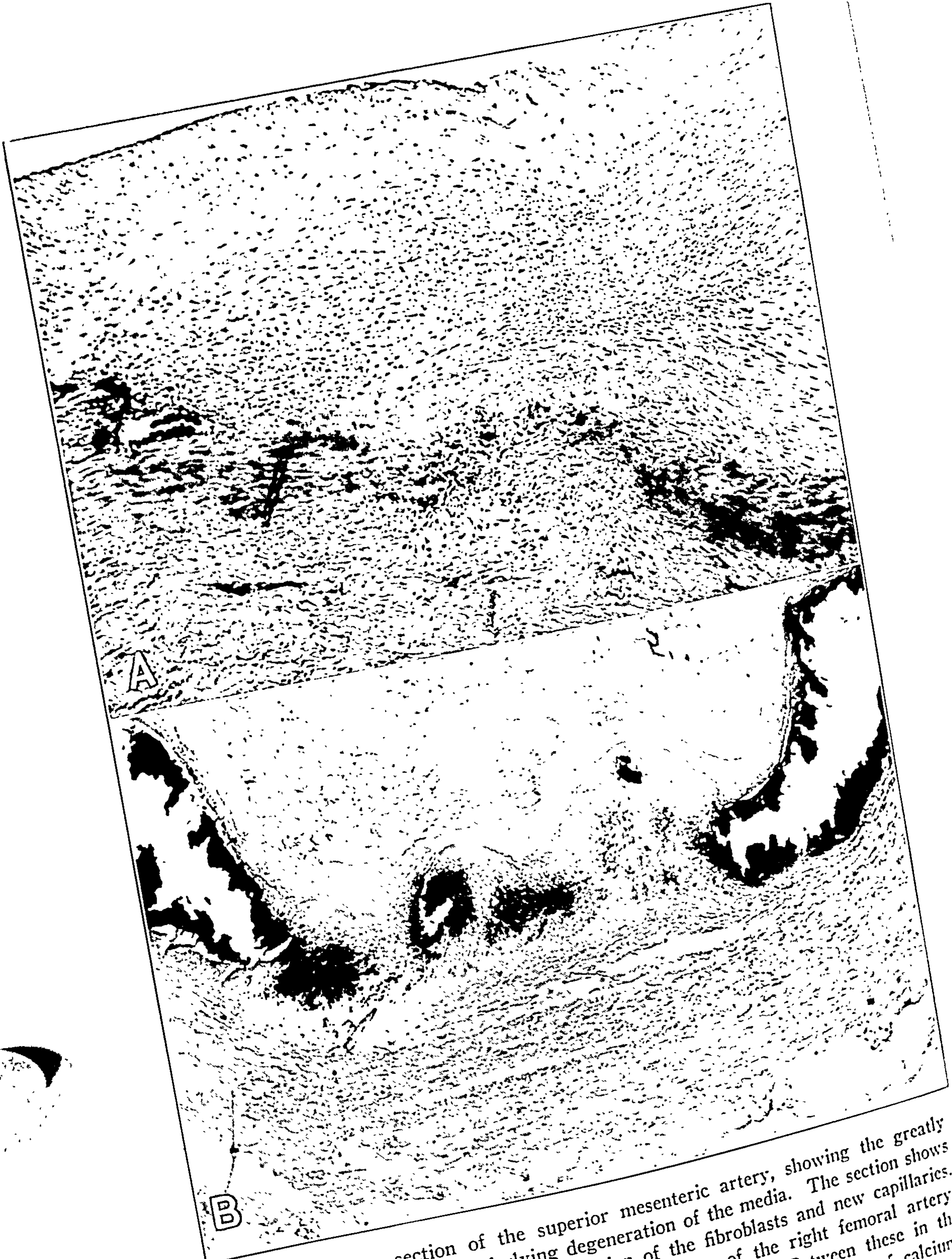

Fig. 4.—*A*, a section of the superior mesenteric artery, showing the greatly thickened intima and the underlying degeneration of the media. The section shows an area of early repair with an infiltration of the fibroblasts and new capillaries. Hematoxylin and eosin stain; × 69. *B*, a section of the right femoral artery. Typical large plaques of calcium are seen in the media. Between these in the muscle bundles and fibrous connective tissue are seen fine granules of calcium. Von Kossa stain; × 41.

and the Warthin-Starey stain for spirochetes were used on a few sections in an unsuccessful attempt to demonstrate micro-organisms.

Microscopically, there was a profound pathologic change present thoughout the media of all the arteries examined. The arterioles showed no pathologic change. The intima was not especially involved in this process. Arteriosclerosis, as represented by deposits of cholesterol and calcification of the intima, was present only to a slight degree. However, the intima was irregularly thickened throughout and had a peculiar undulating character.

The pathologic change taking place in the media was fundamentally one of degeneration. This was present to a profound degree in the muscular vessels. It was characterized by a degenerative change in the muscular fibers, with the result that these fibers appeared to be reduced in number and to be separated from each other by a granular basophilic substance. This substance stained red with thionine and polychrome methylene blue. It contained small droplets of fat when stained with sudan III. It had a finely granular deposit of calcium throughout and hypertrophy of the few remaining muscle fibers, shown in the sections by their increased size. In the muscular arteries the degenerative change had proceeded to a point where there was nearly complete absence of the media in some areas. In these vessels and also in the elastic arteries the elastic fibers were swollen and irregularly fragmented.

Throughout all the vessels there were areas of attempted repair by the formation of fibrous tissue. In the aorta where the degenerative change was the least severe the reparative process was much more satisfactory. As shown in figure 3, there were triangular areas of scar formation with the base toward the intima and extending nearly through to the adventitia. In the smaller arteries areas of repair were frequent (fig. 4*A*). Here there was an invasion of fibroblasts, collagen fibrils and newly formed capillaries into a degenerated portion of the media.

In the arteries of the lower extremities calcareous degeneration of the media was particularly prominent. In accordance with the suggestion of Klotz,[7] the Moenckeberg type of medial sclerosis, so well shown here, and the granular deposits of calcium in the media of the aorta were essentially manifestations of the same process, the calcium granules merely showing different degrees of coalescence. We have endeavored to show this in figure 4*B*. The von Kossa stain here showed not only large plaques of calcification in the media but beginning fine granular calcification in the degenerating muscle bundles and fibrous connective tissue between the plaques.

In the walls of the aneurysms themselves the same degenerative changes were present as were found in the media. In the section in figure 5*A*, which was taken from the wall of the aneurysm in the right subclavian region, a profound degenerative change of both the muscularis and the elastica was evident. The swelling and fragmentation of the elastic fibers could be especially well seen.

In areas in which the lumen of the vessel had been occluded by a ligature the wall of the vessel was replaced by loose connective tissue, which showed an infiltration of lymphocytes and plasma cells with an occasional foreign body giant cell. Such an area is shown in figure 5*B*.

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[7] Klotz, O.: Studies upon Calcareous Degeneration, J. Exper. Med. **8**:322, 1906.

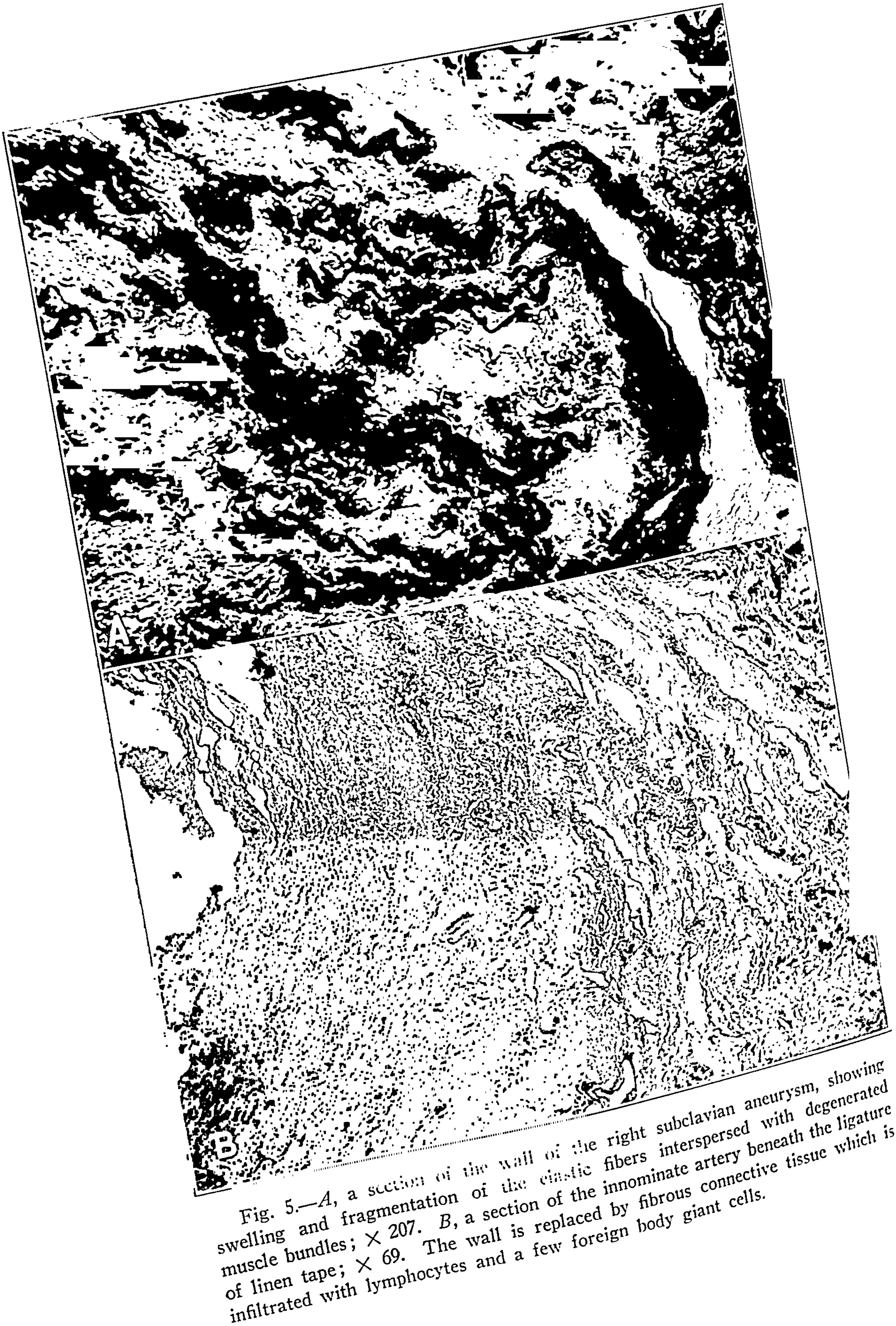

Fig. 5.—*A*, a section of the wall of the right subclavian aneurysm, showing swelling and fragmentation of the elastic fibers interspersed with degenerated muscle bundles; × 207. *B*, a section of the innominate artery beneath the ligature of linen tape; × 69. The wall is replaced by fibrous connective tissue which is infiltrated with lymphocytes and a few foreign body giant cells.

COMMENT

The majority of the cases of multiple aneurysms reported in the literature are either syphilitic or mycotic in origin and as such have no resemblance to the picture herein presented. The small multiple aneurysms associated with periarteritis nodosa have little resemblance to the lesion we have described. Also, the frequently reported cases of multiple aneurysms of the circle of Willis are morphologically and etiologically different.

Literature on diseases of the media is relatively scanty. Scarpa in 1804 has the distinction of being the first to state that no aneurysm could arise without some disease of the media. Francis Welch [8] was not only the first to describe syphilitic aortitis clearly but also the first to describe degenerative lesions of the aorta, unassociated with aneurysm and caused, as he stated, by rheumatism or alcohol. Johnson [9] recognized the existence of hypertrophy of the media, more particularly in the smaller arteries. Thoma [10] laid stress on weakening and degeneration of the media of the aorta and larger arteries as predisposing to sclerosis of the intima. It was Moenckeberg,[11] however, who made the first serious study of disease of the media as a separate entity. Weiszmann and Neumann [12] and Manchot [13] stressed the association of the formation of aneurysms with arteriosclerosis and fatty degeneration of the media, especially of the elastic fibers. Dmitrijeff [14] stated that the fatty degeneration of the elastic fiber is the earliest sign of lesions of this coat.

Klotz,[15] in a monograph on diseases of the media, classified the degenerative lesions of the media under the headings of atrophy, necrosis and fatty, calcareous, amyloid and hyaline degeneration. They are not necessarily associated with disease of the intima. The change is widespread but occurs most severely in the muscular arteries. The degeneration occurs in the muscle fibers but at a later stage may involve the elastic fibers as well. It is in the areas formerly occupied by muscle that calcium and fat are deposited. Whether the calcium occurs in plaques, as described by Moenckeberg and found in this case in the femoral arteries, or is present in fine granules, as seen in the aorta in this case, is dependent, according to Klotz, on the density of the elastic fibers. Klotz stated that whatever the type of degeneration of the media may be, the weakening of this coat provides the physical criteria for the formation of an aneurysm. Although he mentioned no specific cases, he stated that sclerosis of the media is often associated with peripheral diffuse dilatation of the arteries or multiple sacular aneurysms, which are rarely noted at autopsy and do not attain clinical significance.

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[8] Welch, F. H.: Aortic Aneurysm in the Army, Med.-Chir. Tr. **11**:59, 1876.

[9] Johnson, G.: On Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney, Med.-Chir. Tr. **51**:57, 1868.

[10] Thoma, R.: Ueber die Abhängigkeit der Bindegewebsneubildung in der Arterienintima von den mechanischen Bedingungen des Blutumlaufes, Virchows Arch. f. path. Anat. **105**:1, 1886.

[11] Moenckeberg, J. G.: Ueber die reine Mediaverkalkung der Extremitätarterien und ihr Verhalten zur *Arteriosklerose*, Virchows Arch. f. path. Anat. **121**:141, 1903.

[12] Weiszmann, F., and Neumann, S.: Ueber Veränderungen der elastischen Fasern in den Gefässwänden infolge von Arteriosklerose, Allg. Wien. med. Ztg. **35**:291, 1890.

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[14] Dmitrijeff, A.: Die Veränderung des elastischen Gewebes der Arterienwände bei Arteriosklerose, Beitr. z. path. Anat. u. z. allg. Path. **22**:207, 1892.

[15] Klotz, O.: Arteriosclerosis: Diseases of the Media and Their Relation to Aneurysm, Lancaster, Pa., New Era Printing Co., 1911.

More recently the product of the muscular degeneration has been called chromotropic substance by Schultz.[16] Gsell[17] and Erdheim[18] described this type of degeneration in the aorta associated with cyst formation and leading to spontaneous rupture. Moritz[19] and Klotz and Simpson[20] reported similar cases. Cellina[21] reported a disseminated type of the disease occurring in old age.

The etiology of these degenerative changes is as obscure as that of arteriosclerosis in general. That certain bacterial infections can produce disease of the media is well recognized. Foremost among these is syphilis. In our own case this can be ruled out, both clinically and pathologically. The pyogenic bacteria are capable of producing lesions in the media with mycotic aneurysms. There was a history of "blood poisoning" in this case twenty-eight years before death. The lesion in the media, however, is not inflammatory. Wiesel and Löwy[22] pointed out that diphtheria, typhoid, scarlet fever, pneumonia and influenza may be associated with degeneration of the media, but in this case there is no history of these infections.

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[16] Schultz, A.: Pathologie der Blutgefässe, Ergebn. d. allg. Path. u. path. Anat. **280**:65, 1931.

[17] Gsell, O.: Wandnekrosen der Aorta als selbständige *Erkrankung und ihre* Beziehung zur Spontanruptur, Virchows Arch. f. path. Anat. **270**:*1, 1928.*

[18] Erdheim, J.: Medionecrosis aortae idiopathica, Virchows Arch. f. path. Anat. **273**:454, 1929; Medionecrosis aortae idiopathica cystica, *ibid.* **276**:187, 1930.

[19] Moritz, A. R.: Medionecrosis Aortae Idiopathica Cystica, Am. J. Path. **8**:717, 1932.

[20] Klotz, O., and Simpson, W.: Spontaneous Rupture of the Aorta, Am. J. M. Sc. **184**:455, 1932.

[21] Cellina, M.: Medionecrosis disseminata aortae, Virchows Arch. f. path. Anat. **280**:65, 1931.

[22] Wiesel, J., and Löwy, R.: Studien zur Pathologie des Kreislaufs, Wien. Arch. f. inn. Med. **1**:197, 1920.

It has been shown by Klotz[23] and Adler and Hensel[24] that numerous drugs and poisons, for example, nicotine and epinephrine, will produce medial degeneration experimentally in animals. In fact, Klotz produced true multiple aneurysms in rabbits by the long continued injection of epinephrine. The bearing of these observations on the disease in man is not conclusive.

Thayer and Fabyan[25] pointed out that vessels subjected to unusual strain, as the femoral arteries of persons who remain on their feet all day, show similar degenerative changes. It is interesting to note that in this case the aneurysms occurred at a site where the artery passed over an articulation. This is certainly the point where maximum movement in the arterial wall might be expected and where the artery might be subjected to maximum strain.

That old age can produce quantitative and qualitative changes in the elastic tissue has been shown by Aschoff.[26] Our own patient was a relatively young person who showed scant evidence of the arterial changes associated with advanced age.

From the point of view of the surgical treatment of aneurysms, the case presents several matters of interest. First, it emphasizes that the most meticulous asepsis should be employed in all operations of a vascular nature lest infection ensue and give rise to secondary hemorrhage. In this case the first aneurysm attacked was already infected due to sloughing of the skin over it, and from this area moderately severe secondary hemorrhage occurred, for which it was necessary to remove the clot from the aneurysm and ligate the vessel again.

The second aneurysm attacked was that in the right subclavian region, for the cure of which the innominate artery was ligated, while the wound of the infected aneurysm in the left femoral region was still draining. This wound became infected also; it was treated with diluted solution of sodium hypochlorite, U. S. P., and healed, but subsequently the infection recurred and gave rise to severe secondary hemorrhage which, however, was satisfactorily controlled by packing.

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[23] Klotz, O.: Experimental Production of Arteriosclerosis, Brit. M. J. **2**:1767. 1906; Experimentelle Arbeits-Arteriosklerose, Centralbl. f. allg. Path. u. path. Anat. **19**:535, 1908.

[24] Adler, I., and Hensel, O.: Intravenous Injections of Nicotine and Their Effects upon the Aorta of Rabbits, J. M. Research **15**:229, 1906.

[25] Thayer, W. S., and Fabyan, M.: Studies on Arteriosclerosis, with Special Reference to the Radial Artery, Am. J. M. Sc. **134**:811, 1907.

[26] Aschoff, L.: Ueber Atherosklerose und andere Sklerosen des Gefässystems, Beihefte z. Med. Klin. **4**:1, 1908.

Another point of surgical interest is the effect of the ligatures on the walls of the vessel, as in this case all ligations were performed with linen tape ½ inch (1.3 cm.) in width and tied just tightly enough to obliterate the pulsation in the vessel distal to the ligature. At postmortem examination all ligatures were intact except that placed on the right common iliac artery, which had obviously cut through the wall of the artery, giving rise to the aneurysm, rupture of which was the immediate cause of death. Histologic study of the arteries at the site of ligation showed that the ligatures in all instances had caused necrosis of the underlying vessel wall with replacement by fibrous tissue.

From the standpoint of the physiology of the circulation in the periphery after ligation of the major vessel to an extremity, it is interesting to note that during the relatively long period which elapsed between the appearance of the aneurysms and the vascular ligations, a sufficient collateral circulation developed so that there was little change in skin temperature distal to the ligature and no signs of circulatory insufficiency so long as the patient remained prone. However, cyanosis promptly appeared when the venous pressure was raised by the patient assuming a sitting posture.

The long period between the successive ligation of the left iliac, innominate, right iliac and left subclavian arteries was probably responsible for the fact that no clinical evidence of cardiac change was demonstrable. The constant blood pressure is no doubt to be explained on the same basis. It should be noted in this regard, however, that the patient remained in bed at absolute rest for almost his entire stay in the hospital with the least possible load on his circulatory system.

The immediate cause of death was the rupture of an aneurysm of the left common iliac artery, brought about by the giving way of the wall at the site of ligation with a linen tape. Why this ligature should have cut through when the left iliac and innominate arteries, which had been ligated for a much longer time, remained intact is something of a mystery and yet stresses the danger inherent in ligation of large arteries. The wall of a large artery beneath a ligature always undergoes necrosis and replacement with fibrous tissue. If this replacement takes place rapidly enough and the pressure within the vessel is not too great, the ligation is successful; but here it is evident that such was not the case—the ligature cut through and gave rise to a fatal hemorrhage.

SUMMARY

A case of multiple aneurysm of the major peripheral arterial trunks is reported. The basic pathologic change responsible for the aneurysm was a degeneration of the tunica media characterized by loss of muscle

fibers, swelling and fragmentation of elastic fibers, disseminated foci of calcification and fibrous replacement of the media. Some fibrous thickening of the intima was also present. The process, which differs from nodular intimal arteriosclerosis and shows no evidence of inflammation, is probably related to the medial arteriosclerosis of Moenckeberg.

In the treatment of the aneurysm, all the primary branches of the aorta leading to the head and extremities, except the left carotid artery, were successively ligated. Some studies on the effects of these ligations on the peripheral circulation are presented.

ANHYDREMIA AS A FACTOR IN DEATH FROM AUTOLYTIC PERITONITIS

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In 1924 Mason and Davidson published reports of experiments which directed attention to the toxic effect of fresh liver implanted in the peritoneal cavity. Later Ellis and Dragstedt[1] (1930) repeated this work and came to the conclusion that the death of the animals in which liver had been placed in the peritoneal cavity was due to the severe peritonitis caused by an organism similar to Bacillus Welchii. Peritonitis did not occur when pieces of adult or fetal liver which had been autoclaved were introduced into the abdomens of dogs. According to these authors the infection came from the liver in which the bacteria persisted in a latent state until stimulated to activity by the asphyxia of the liver tissue.

Andrews and Hrdina[2] repeated these experiments, as they did not believe that when animals died in so short a time (from twenty to twenty-four hours) death could be attributed to infection alone. In spite of the fact that they recovered an organism similar to B. Welchii from the implanted liver and fluid in the abdomen, they believed that the death of the animal was due to the toxic action of the autolyzed liver tissue. The changes which were noted after death were hemorrhage into the peritoneum and free fluid in the abdominal cavity (from 300 to 500 cc.). Death was thought to be caused by a severe infection from a gas-producing organism, which probably entered the abdominal cavity through an altered intestinal wall, for such an infection may follow also implantation of sterile material. The toxic agent derived from autolyzed liver is soluble in water, is thermostable, is precipitated by alcohol and chloroform, gives a biuret reaction and is dialyzable with difficulty. Therefore, it is probably to be classified among the albumoses.

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[1] Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, Arch. Surg. **20**:8-16 (Jan.) 1930.

[2] Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. **52**:61-66, 1931. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of Bacillus Welchii Infections in Dogs by Injection of Sterile Liver Extracts or Bile Salts, ibid. **53**:176-181, 1931.

Vallone[3] performed a series of experiments in which pieces of different organs and tissues (liver, spleen, pancreas, muscle and kidney) were placed in the abdominal cavity in the fresh state after being autoclaved. The most striking change which was noted in all the experiments was an intense hyperemia of the peritoneum, the presence of varying amounts of a serohemorrhagic fluid and a more or less definite fatty change in the liver and spleen. The cultures from the fluid in the abdominal cavity and implanted material (simple and Tarozzi's broth) were negative. In almost all the cases the implanted tissue was encapsulated by the great omentum. Vallone thought that homo-implants and hetero-implants into the abdominal cavity caused grave symptoms because of the absorption of protein materials following necrosis. These substances are not inactivated by heat, and death follows, even when the implants have been autoclaved. Applying his experimental results to the clinic, he expressed the belief that death in some cases of acute pancreatitis and in some cases of abdominal contusion in which the hemorrhage is not large enough to cause death can be explained on the basis of the absorption of products from contused organs, such as the liver, spleen and kidney. The clinical syndrome in some of these cases is not unlike that which can be produced experimentally.

Mason and Lemon[4] continued work along this line. The results of their experiments caused them to believe that three factors contributed to death from autolytic peritonitis. The first is a toxic substance formed in the liver during autolysis, since from 7 to 8 cc. of a saline extract given intravenously is enough to produce death of the experimental animal. The second factor, which Mason and Lemon mentioned and Ellis and Dragstedt overemphasized, is the Welch bacillus, for a pure culture of this organism injected into the peritoneal cavity does not produce changes comparable to those found after the autolysis of the liver. The third factor is anhydremia. Free fluid is always found in the peritoneal cavity of dogs which have died after implantation of liver into the peritoneum. The quantity of free fluid is equal to from one third to one half of the total volume of blood. With the escape of fluid into the peritoneal cavity, these authors noted considerable increase in the concentration of the blood, due to a reduction in the volume of blood plasma and blood serum and an increase in the percentage of fibrin.

Mason and Lemon stated that their experiments justified them in assuming that the liver tissue autolyzed in the peritoneal cavity liberated substances which cause a chemical peritonitis followed by an increased permeability of the abdominal viscera and that the use of drains shortened rather than lengthened the life of the animals.

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[3] Vallone, D.: La peritonite autolitica consecutiva a trapianto nell'addome di organi e di tessuti, Riforma med. 47:1293-1297 (Aug. 24) 1931.

[4] Mason, E. C., and Lemon, C. W.: Anhydraemia as a Possible Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. 55:427-431, 1932.

In 1935 I[5] published the results of work which I had done on this subject. I experimented on rabbits, implanting into their abdominal cavities varying quantities of liver tissue recently removed under sterile conditions from animals of the same species. I demonstrated that the rabbit's liver does not contain the Welch bacillus or other pathogenic organisms to which have been attributed the cause of death of animals into which liver tissue has been implanted. I also demonstrated that not all the rabbits into which liver had been implanted died within a few hours and that the death of the animals was not in direct or close relation to the amount of liver implanted. The peritoneal fluid found in the animals which died a short while after implantation was sterile.

In my work cultures from the liver, spleen and bone marrow were always positive for the colon bacillus, even when cultures of the fluid in the peritoneal cavity were negative. The presence of these organisms in the liver, spleen and bone marrow—not normally found there—would indicate that they had probably passed through the intestinal wall at points adherent to the implanted liver, where there were gross and microscopic evidences of inflammation, and then entered the blood stream to be deposited in the liver, spleen and bone marrow. When these foci of inflammation were not present the animal did not die. The presence of colon bacilli cannot be regarded as a preagonal phase, because they were found before the beginning of this phase. Neither can their presence be regarded as due to contamination during operative manipulations, for if such were the case the peritoneal fluid would have been infected, but it was always sterile. Very small amounts of peritoneal exudate were found in the rabbits which died a short while after the implantation of homologous liver, while Andrews and Hrdina found from 300 to 500 cc. in their animals. Vallone and Mason and Lemon found relatively large quantities. According to Mason and Lemon the peritoneal fluid equals from one third to one half of the blood volume of the animal, and therefore anhydremia cannot be considered the cause of death. Having noticed that there were but a few drops of fluid in the peritoneal cavity of the rabbits which had died soon after the introduction of fresh liver, I undertook other experiments in which dogs were used in order to repeat the experiments of the American authors and to study the relation of anhydremia to death. The data on these experiments are given in the accompanying table.

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[5] Iesu, G.: Ricerche batteriologiche sulla peritonite autolitica, Gior. di batteriol. e immunol. **15**:109-120, 1935.

EXPERIMENTAL WORK

In these experiments the same operative technic was employed as on the rabbits. A median laparotomy was performed under aseptic precautions, and a piece of liver that had been removed from another dog and previously weighed and sterilized was dropped into the abdominal cavity. The abdominal incision was then closed. All the dogs with the exception of the sixth showed weakness after five or six hours, which increased with time up to death.

Examination of the blood (Wu method) showed an increase in the percentage of fibrin, which in experiment 4 increased from 3.5 before the operation to 7.25 sixteen hours after.

The autopsy performed on some animals in the preagonal state showed a serohemorrhagic fluid (from 310 to 600 cc.) in the peritoneal cavity and evidences of a hemorrhagic enteritis, diffuse peritonitis and fatty degeneration of the spleen and liver. The implanted piece of liver was reduced in size and of a brown color. Adhesions were found between the piece of liver and the mesentery of the small bowel, the anterior wall of which in one animal presented areas of necrosis. A piece of the liver which was implanted was placed in simple and Tarozzi's broth in all the experiments to determine whether or not it was free from germs. The cultures were constantly sterile. The results confirm the conclusions of Wolbach and Saiki, Vallone, Berg, Zau and Jobling and Trusler and Reeves [6] that liver of the living dog does not contain pathogenic organisms. On the other hand, the free fluid in the peritoneal cavity, of which I have made cultures (simple and Tarozzi's broth), has always contained numerous intestinal bacteria. I have never found, however, B. Welchii or similar bacteria.

Data on Experimental Work

Experiment No.	Wt., Kg.	Implanted Liver, Gm.	Percentage of Implanted Liver	Length of Time Before Death	Blood Volume	Quantity of Peritoneal Fluid, Cc.	Approximate Relation
1.....	15.5	80	0.50	25 hr.	1.192	400	1/3
2.....	21.5	110	0.50	19½ hr.	1.653	400	1/4
3.....	15.93	175	0.10	16 hr.	1.220	600	1/2
4.....	12.8	50	0.39	26 hr.	0.987	310	1/3
5.....	15.4	80	0.51	24 hr.	1.187	400	1/3
6*...	16.2	69	0.37	48 days	1.246	none	...

* The implanted piece of liver was encapsulated by the great omentum.

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[6] Trusler, H. M., and Reeves, J. R.: The Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis: Bacterial Flora of Liver and Muscle of Normal Dogs, Arch. Surg. **28**:479-491 (March) 1934. Trusler, H. M.; Reeves, J. R., and Martin, H. E.: Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis: A Bacteriologic Study of the Peritoneal Exudates, ibid. **30**:371-393 (March) 1935.

COMMENT

My work confirms that of Andrews and Hrdina, Vallone and Mason and Lemon. Like these, I have found relatively large quantities of peritoneal fluid and a considerable increase in the concentration of blood, with lowering of the volume of blood plasma and blood serum and an increase in the percentage of fibrin.

Cultures from the implanted liver have never shown B. Welchii to which the death of the animal could be attributed. Some authors (Wolbach and Saiki, Trusler and Reeves and others) have found an anaerobic bacillus in cultures taken from the liver. This organism produces gas, is gram-positive, does not ferment sugar, does not produce endotoxins and when injected into the muscles of guinea-pigs is not pathogenic. It has been confused with pathogenic bacilli. Too frequently anaerobic, gas-producing organisms have been regarded as B. Welchii. These authors expressed the opinion that this mistake has been made frequently and that some workers, such as Ellis and Dragstedt, have as a result considered B. Welchii and similar organisms as the lethal factor.

Mason and Lemon injected a pure culture of B. Welchii into the peritoneal cavities of dogs, and their results were in no way comparable to those found in the autolytic peritonitis under discussion. The fact that the peritoneal reactions can be produced by implants of sterile liver speaks against the peritoneal change being bacterial in origin (Andrews and Hrdina, Vallone and Trusler and Reeves).

The results obtained in my experiments would seem to show that the theory of a bacteremia developing from the liver transplant is tenable neither for dogs nor for rabbits. However, they confirm the theory of a chemical peritonitis, which causes an increase in the permeability of the abdominal viscera and considerable free fluid in the peritoneal cavity. The bacteria in the fluid are of intestinal origin. They have been demonstrated by Mason and Lemon.

Anhydremia following the implantation of pieces of liver in the abdominal cavity cannot be regarded as a *constant* cause of death, for in my work I have shown first in rabbits and then in dogs that under identical conditions the rabbits died in the *same* length of time as the dogs, even when there was so little fluid in the peritoneal cavity as to preclude anhydremia as a factor in the cause of death.

DISCHARGES FROM THE NIPPLE

THEIR CLINICAL SIGNIFICANCE AND MAMMOGRAPHIC INTERPRETATION

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AND

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OMAHA

Nature frequently enshrouds pathologic changes of the mammary gland in a group of confusing symptoms. Correct interpretation of these inconstant and ever changing syndromes sorely taxes the diagnostic ingenuity of the physician. No two persons react similarly to identical lesions. A papilloma of the milk ducts may initiate a bloody discharge from the breast of one patient and a serous secretion from the breast of another, while there may be no discharge from the breast of a third patient. Likewise, a small infiltrating deep-seated carcinoma may be distinct and easily palpable in one breast and indefinite and indeterminable in another. Pain may or may not announce the presence of an intracystic hemorrhage, a growing neoplasm, a distended cyst or an infection of the milk ducts.

A discharge from the nipple of a nonlactating breast is frequently the initial symptom which impels the patient to seek medical advice. While the abnormal discharge is indicative of a pathologic change within the ductal and secretory systems, it affords but scant information concerning the provocative factor. It is evident that the amount, color, consistency and odor of the discharge depend not only on the nature of the causative lesion but on the degree to which the secretion is altered before reaching the surface of the nipple. If the bleeding neoplasm is situated near the orifice of the duct, the escaping fluid is frankly hemorrhagic, but if the tumor is deep within the matrix, the fluid assumes a serosanguineous or a serous character or even a brownish chocolate color due to the degeneration of the retained blood and its admixture with other secretions from the duct. The character of the discharge may also be altered by infection, necrosis or extension of the causative lesion. For example, a simple cyst may produce a clear serous secretion, but if a cyst is invaded by pathogenic organisms, the discharge assumes a purulent character.

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Unfortunately, conditions which produce these confusing discharges likewise fail to establish identifying physical signs. In spite of the accessibility of the mammary glands, small infiltrating carcinomas, papillomas, dilated lactiferous ducts and compressible cysts can seldom be palpated. An appreciation of these diagnostic difficulties caused Cutler[1] to introduce his transillumination studies. While some neoplasms can be visualized by this procedure, the vast majority possess the same translucency as the matrix of the breast, thus making differentiation extremely difficult. Soft tissue roentgenography, as popularized by Lockwood and Stewart,[2] has also failed to depict the identifying characteristics of mammary neoplasms clearly. The frequency with which exploratory biopsy is performed confirms the foregoing statements.

All pathologic conditions associated with a discharge from the breast must, of necessity, originate within or secondarily involve the ductal system. Any procedure, therefore, which actually visualizes the lactiferous ducts should possess considerable diagnostic value. During the past two years a method has been developed for visualizing the breast by means of contrast roentgenograms.[3] A radiopaque material, such as stabilized thorium dioxide, is introduced into the milk ducts by cannulating their orifices with a blunt no. 26 gage needle. Stereoscopic roentgenograms then give an accurate anatomic pattern of the ducts. Any abnormalities, such as alterations in the size, shape or conformation of these ducts, can be detected readily and the causative agent identified. An experience with more than three hundred and seventy-five contrast mammograms clearly demonstrates that they are invaluable in the diagnosis of lesions of the breast. Mammographic studies are particularly effective in visualizing pathologic states which are responsible for discharges from the nipple, and they also contribute valuable information concerning the evolution of such syndromes. Corroborative evidence can best be furnished by the presentation of actual cases.

BLOODY DISCHARGES

A frank hemorrhagic or serosanguineous discharge from the nipple indicates that the mammary gland is undergoing some pathologic change. While such a symptom constitutes a definite warning, unfortunately it is associated with such a variety of pathologic conditions that it possesses but little diagnostic value. Stowers[4] concluded that a bloody discharge occurring in the absence of trauma or a palpable tumor is most likely to be caused by a papilloma of the milk ducts. Adair[5] expressed the belief that it is indicative of a carcinoma of the milk ducts. Tapie[6] stated that such a loss of blood is due to a benign papillomatous growth or to an "endocaninular dendritic carcinoma." Greenough and Simmons[7] studied twenty cases of cystadenoma and found that in eleven there was a hemorrhagic seepage from the nipple; a malignant growth was discovered in three. Miller and Lewis[8] maintained that a bleeding nipple is not necessarily a sign of a malignant growth, for the discharge may originate in an adenocystic disease of the breast. Cheatle and Cutler[9] pointed out that such a discharge is usually associated with a papilloma, but that it affords no information as to whether the tumor is benign or malignant. Von Saar[10] firmly maintained that there is no relationship between a malignant lesion of the breast and a bleeding nipple. Paget's disease, tuberculosis, chronic cystic mastitis,[11] fibro-adenoma, trauma and vicarious menstruation[12] are other conditions associated with a hemorrhagic discharge from the milk ducts.

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[1] Cutler, Max: Transillumination as an *Aid in the* Diagnosis of Breast Lesions, Surg., Gynec. & Obst. **47**:*721, 1929.*

[2] Lockwood, I. H., and Stewart, W.: The Roentgen Ray *Examination* of the Breast, J. Missouri M. A. **29**:*557, 1932.*

[3] Hicken, N. Frederick: Mammography: The Roentgenographic Diagnosis of Breast Tumors by Means of Contrast Media, Surg., Gynec. & *Obst.* **64**:593 (March) *1937.* Hicken, N. Frederick; *Best,* R. Russell; Moon, C. F., and Harris, T. T.: The Preoperative Visualization of Breast Tumors, J. A. M. A. **108**:864 (March 13) *1937.*

One is forced to admit that the symptom of a "bleeding nipple" has no diagnostic significance, yet it is imperative that the primary cause be accurately determined. Contrast mammographic visualization of the ducts is effective in locating the offending neoplasm, as is evidenced by the following cases.

Papilloma.—Mrs. P. P., a housewife aged 44, entered the hospital because of a "bleeding breast." Six weeks previously, while adjusting her brassiere, she observed a serosanguineous secretion escaping from the left nipple. This was repeated daily. There were no pains, tenderness or history of trauma. She had successfully nursed each of her three children, the youngest of whom was 2 years of age.

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[4] Stowers, J. E.: Significance of Bleeding or Discharge from the Nipple, Surg., Gynec. & Obst. **61**:537, 1935.

[5] Adair, F. E.: Sanguineous Discharge from the Nipple and Its Significance in Relation to Cancer of the Breast, Ann. Surg. **91**:197, 1930.

[6] Tapie, Pierre: The Bleeding Nipple, M. J. & Rec. **121**:537 (May 6) 1925.

[7] Greenough, R. B., and Simmons, C.: Papillary-Cystadenomata of the Breast, Ann. Surg. **45**:188, 1907.

[8] Miller, E. M., and Lewis, Dean: The Significance of a Sero-Hemorrhagic or Hemorrhagic Discharge from the Nipple, J. A. M. A. **81**:1651 (Nov. 17) 1923.

[9] Cheatle, G. L., and Cutler, Max: Tumors of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment, London, Edward Arnold & Co. 1931. Cutler.[1]

[10] von Saar, G.: Ueber Cystadenoma mammae und Mastitis chronica cystica, Arch. f. klin. Chir. **84**:223, 1907.

[11] Lewis, Dean, and Geschickter, C. F.: Ovarian Hormones in Relation to Chronic Cystic Mastitis, Am. J. Surg. **24**:280, 1934.

[12] Hirschberg, A.: Ueber die vikariierende bzw. komplementäre Menstruation, Centralbl. f. Gynäk. **38**:929, 1914.

The breasts were small, atrophic and soft. There were no points of localized tenderness such as are sometimes seen with a papilloma, and no tumor could be palpated. Several subareolar milk ducts were dilated, and on compression two drops of bright red blood escaped from one centrally placed duct and a serous secretion escaped from its neighbors. Transillumination and soft tissue roentgenograms failed to locate the pathogenic lesion.

A hemorrhagic discharge was the only presenting symptom, and no abnormal physical signs could be found. In all probability a papilloma of the milk ducts was the causative lesion, but such a diagnosis was entirely conjectural. In order to obtain definite information, mammographic visualization was employed. The bleeding duct was cannulated with a blunt no. 26 gage needle, and 2 cc. of colloidal thorium dioxide was introduced. The stereoscopic roentgenograms gave an accurate pattern of the ducts in the diseased lobule. The nipple portion of the duct was smooth, regular and of uniform diameter, but the ampullar segment contained a "negative shadow" or "filling defect." This was interpreted by Dr. H. B. Hunt as being a pedunculated tumor which protruded into the ductal lumen and displaced the contrast medium (fig. 1). The ramifying lacteal ducts and acini were

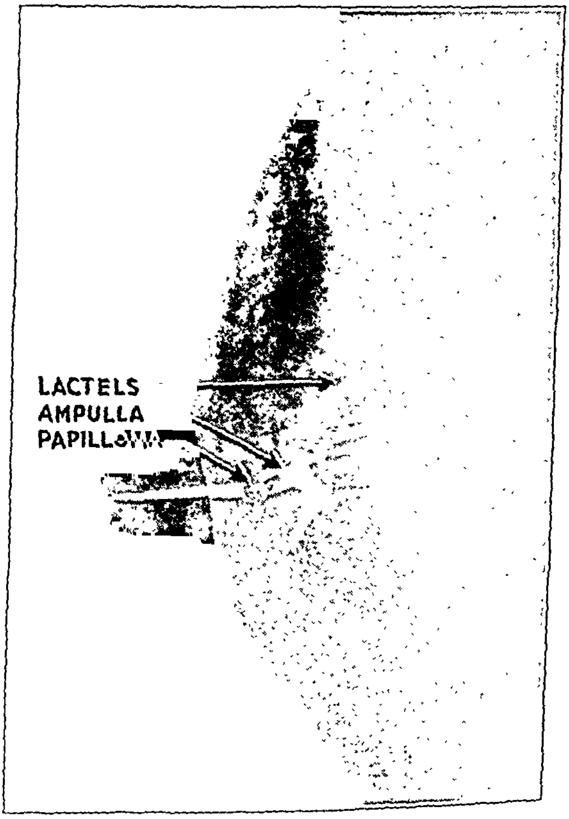

Fig. 1.—Mammogram in a case of papilloma, showing the bleeding duct visualized by the injection of 2 cc. of colloidal thorium dioxide. The papilloma appears as a "negative shadow" in the ampulla.

clearly visualized and presented a normal pattern. The hemorrhagic discharge, the absence of a palpable tumor and the roentgenographic silhouette of a localized, noninfiltrating, pedunculated neoplasm arising from the wall of a lactiferous duct characterized this tumor as being a benign papilloma (fig. 2).

Because the neoplasm was situated near the base of the nipple, making it technically impossible to excise the diseased lobule without injuring the neighboring duct, simple mastectomy was performed. Macroscopic examination demonstrated a papilloma the size of a pea arising from the wall of the duct. At the tip of one of the papilliferous projections a small bleeding point was seen, which accounted for the hemorrhagic discharge. Morphologically, the tumor was classified as a benign papilloma.

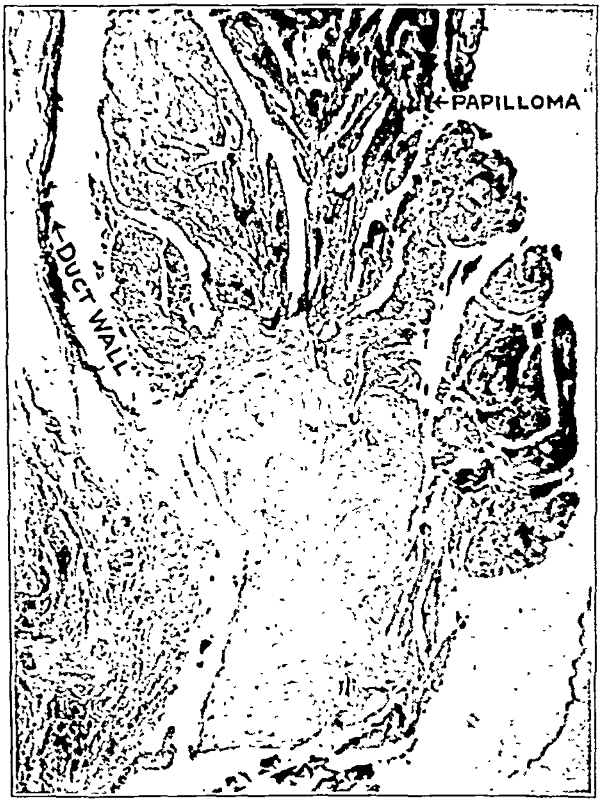

Fig. 2.—Photomicrograph of the offending papilloma.

The mammographic studies accurately located the offending tumor and so clearly revealed its identifying characteristics that the correct diagnosis was made preoperatively. Such results are not fortuitous, for in six other instances definite contrast silhouettes of the provocative papillomas were obtained by stereoscopic mammograms.

Carcinoma.—Mrs. K. K., a housewife aged 38, was worried about a lump in her breast associated with a bloody discharge from the nipple. After the birth of her baby, now 18 months old, a "caked breast" developed. The soreness soon subsided, but the hard, firm mass persisted and steadily increased in size. Three months before the present examination a serohemorrhagic discharge escaped from the right nipple.

Examination disclosed a firm, fixed tumor mass occupying the upper outer quadrant of the right breast. A bloody discharge was escaping from one centrally placed duct and a clear serous fluid from several of its contiguous mates. The tumor mass was not translucent but cast a hazy indefinite shadow. The right axilla contained several small, hard, discrete lymph nodes. Clinically, this appeared to be an advanced carcinoma which had metastasized to the regional lymph glands. In order to see what changes had taken place in the respective lactiferous ducts, a mammogram was made. The bleeding orifice was cannulated and 2 cc. colloidal thorium dioxide was injected into it. The roentgenographic silhouette showed the outer segment of the duct to be normal, but the tumorous portion resembled a filamentous cobweb (fig. 3 *A*). Not only had the infiltrating neoplasm invaded the ducts and thus reduced the size of their lumens, but the rapidly growing malignant cells had distorted, displaced and even destroyed a number of communicating radicals. Hence, the hemorrhagic discharge was produced by a destructive, invasive degenerating type of tumor.

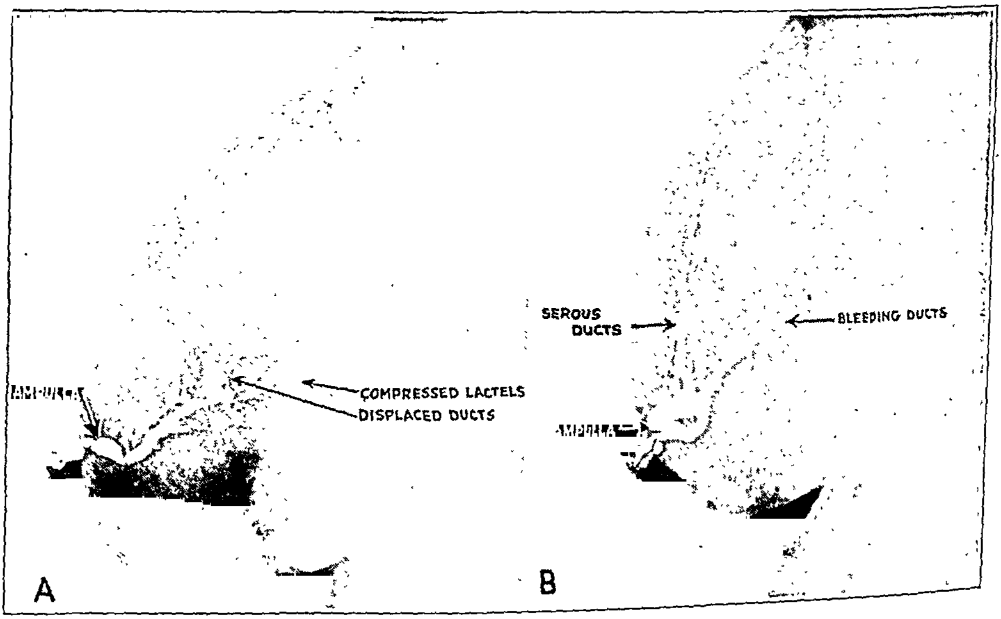

Fig. 3.—Mammograms in a case of carcinoma. *A* shows a bleeding duct into which 2 cc. of colloidal thorium dioxide was injected. The outer segment of the duct is smooth, tortuous and dilated; the inner portion has but few communicating ducts, for they have been destroyed, displaced and compressed by the malignant tumor. *B* shows a duct emitting a serous secretion. Colloidal thorium dioxide was used for the medium. The same destructive process is present as was observed in the bleeding duct, but it is not so far advanced.

The difference between the duct pattern of a papilloma and an invasive carcinoma is so striking that one has no difficulty in determining the cause of the bloody discharge.

SEROUS DISCHARGE

Patients have a tendency to consider a serous discharge from the nipple as being inconsequential, when in reality it may be associated with a grave pathologic condition. Gross[13] reported that a thin, watery, straw-colored fluid escapes from the breast in 10 per cent of all cases of sarcoma. Stowers[4] pointed out that a unilateral serous secretion frequently accompanies a mild infection of the lactiferous ducts. Deaver and McFarland[14] found that 25 per cent of their patients with intracystic papilloma complained of such a discharge. Adair[5] maintained that a watery serous fluid is frequently associated with a carcinomatous neoplasm. In our experience a carcinoma does not give rise to any pathognomonic discharge. At first the secretion may be serous, but as the tumor undergoes degenerative changes it may become hemorrhagic. Likewise, a mammary cancer may emit a serosanguineous discharge from one duct and a clear serous secretion from its neighbors.

It is obvious that a person complaining of a spontaneous emission of serum from the nipple has ample cause to worry. Every possible diagnostic procedure should be employed until an accurate diagnosis can be made. The following cases demonstrate that mammographic visualization of the discharging milk ducts give valuable information concerning the pathogenesis of the abnormal secretions.

Cancer with a Serous Discharge.—In the second case reported a frank hemorrhagic discharge escaped from one centrally placed duct and serous fluid from the other. The mammogram of the bleeding duct showed an invasive carcinoma which had obstructed, displaced and destroyed the regional lacteal ducts. In order to visualize the pathologic process which was responsible for the serous secretion, a comparative mammogram was made by injecting 3 cc. of colloidal thorium dioxide into one of these ducts. The same characteristic deformities were observed in the duct emitting the serous secretion as in its bleeding mate, but not to such a marked degree (fig. 3 *B*). Many of the smaller lacteal ducts were visible, less destruction had taken place and the degenerative process was not so advanced, for the duct into which the medium was injected occupied the periphery of the lesion where the vascular supply was intact.

This case clearly demonstrates that the nature of the escaping secretion may be altered as the pathologic condition pursues its evolutionary cycle.

Postlactation Involvement.—Mrs. L. McC., a housewife aged 28 years, had observed a bright bloody discharge from the right breast and a few drops of a clear serous fluid escaping from the left nipple. There was no pain, tenderness or abnormal sensation. She had nursed each of her four children, the youngest being 2 years of age. During each period of lactation she had produced large quantities of milk. In fact, the breasts had to be partially decompressed between nursing intervals in order to prevent the milk from spontaneously escaping from the ducts.

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13. Gross, cited by Greenough and Simmons.[7]

14. Deaver, J. B., and McFarland, J.: The Breast: Its Anomalies, Its Diseases and Their Treatments, Philadelphia, P. Blakiston's Son & Co., 1917.

On examination, both breasts were found to be large, pendulous and firm. A stripping massage of the right nipple expressed bright red blood from one duct, while a serous secretion was expressed from six ducts of the left breast. The subareolar ducts were dilated, but no abnormalities were detected in either gland. The serous secretion was composed of a clear homogeneous fluid laden with degenerating epithelial cells, a few droplets of oil and an occasional leukocyte. No bacteria were present.

A contrast mammogram of the right breast demonstrated the presence of a bleeding papilloma. In order to ascertain the cause of the serous discharge from the left breast, thorium dioxide was introduced into the offending ducts. The stereoscopic mammogram gave a striking pattern of the entire ductal system. The ducts ramified the matrix in an evenly distributed manner. The ampullae were dilated, and one or two had begun to undergo cystic degeneration. The achitectural arrangement of the smaller lacteal ducts and acini was normal, thus eliminating the presence of any neoplasm (fig. 4). Such a ductal pattern is characteristic of a multiparous gland in a state of secretory quiescence. The escaping serous fluid merely represents the products of desquamation from an enormous ductal system. In this particular case there was no evidence of an incipient malignant growth. Undoubtedly the slight localized dilatation of the ampullae was due to a retention of the desquamative products.

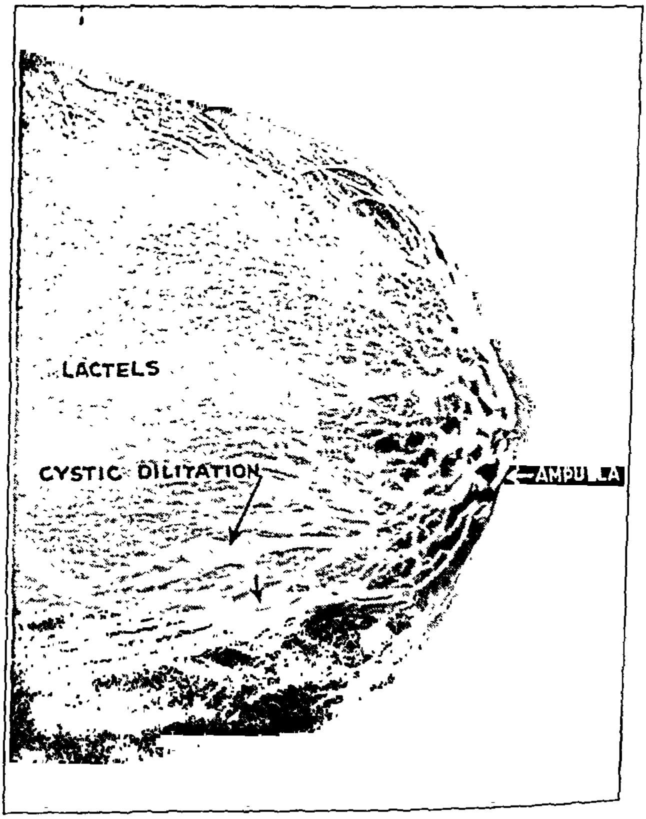

Fig. 4.—Mammogram of an involuting breast. Lipoiodine-Ciba (ethyl) diiodobrassidate) was injected into six ducts. Note the tortuous ampullae, the uniform dispersion of the ducts and the localized areas of ductal dilatation (normal involuting breast).

The right breast was excised because of the papillomatous growth, and the patient insisted that the left one be removed for cosmetic reasons. Macroscopic and histologic studies of the latter confirmed the mammographic diagnosis of postlactation involution.

The second and third cases emphasize the value of the visualization studies, for in one instance the serous discharge was associated with a carcinoma and in the other it was merely the normal response of the multiparous breast.

GREENISH WHITE DISCHARGE

Occasionally a patient desires to know the significance of a thick greenish white discharge which spontaneously escapes from the breast. Unfortunately, this symptom has no diagnostic significance but may be associated with a number of conditions, such as a desquamative cyst, an infected cyst or postlactation involution. The pathogenesis depends on the functional status of the breast, the type of lesion present, the age of the patient and the presence of infection. There is some question as to whether the bacteria, when present, irritate the epithelial lining of the ducts and accentuate the desquamative process or whether they are merely harmless saprophytes. The following cases are instructive.

Infected Cyst.—Mrs. G. G., a housewife aged 29, sought advice because of a bilateral mastalgia associated with a "pussy discharge" from the breast. She had been able to nurse each of her two children, the youngest of whom was 2½ years of age. Three months previously she first experienced distressing pains in both breasts, which were particularly annoying just preceding the menstrual flow. During the past month a thin whitish green discharge seeped from the right nipple, and the breast was so sore and tender that she was unable to wear her brassiere. Hot fomentations and energetic therapy with theelin proved ineffectual. Eight days before the present examination she discovered a hard, firm, tender lumph in the right axilla.

On examination both mammary glands were small and atrophic but extremely tender. The right breast was particularly painful. Several small, discrete tender nodules were scattered throughout both matrices. Gentle massage of the right nipple expressed a thick whitish fluid, which was laden with gram-positive diplococci, degenerating leukocytes and numerous epithelial cells. Both breasts were translucent, and roentgenograms did not demonstrate any abnormalities.

The whitish green discharge, the multiple nodules and the intense mastalgia suggested the diagnosis of cystic degeneration of the breast with coincidental infection. In order to obtain a visual concept of the altered ducts, a contrast mammogram was made. Colloidal thorium dioxide was injected into the orifices of the discharging lacteal ducts, and the resulting stereoroentgenogram presented an accurate reproduction of the diseased ducts. The ampullae were small and of a uniform diameter, and the ducts were evenly dispersed throughout the matrix. In one area a confluence of several ducts formed a large cyst (fig. 5). Its walls were smooth, and there was no evidence of an infiltrating or papillomatous tumor. When the cystic cavity was distended with thorium dioxide, it was definitely palpable and exquisitely tender. In other portions of the breast small cysts were just beginning to form, and the pathologic process seemed to involve the entire gland.

The mammogram clearly showed that the ducts were undergoing a cystic degeneration, and the nature of the escaping discharge indicated that the milk ducts and their cysts had become secondarily infected. These were not true retention cysts, for they still communicated with the regional ducts. Because such a process is not malignant, it was thought that conservative therapy, such as the application of hot fomentations, the administration of theelin and thyroid extract and general systemic stimulation, might give her some relief. This assumption was based on the fact that the cysts had adequate drainage through the patent ducts.

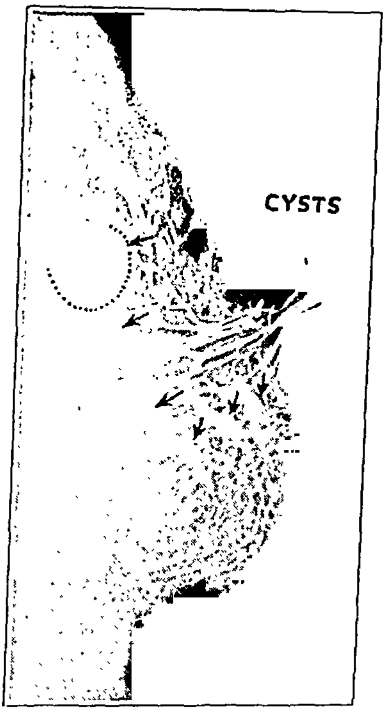

Fig. 5.—Mammogram in a case of multiple cysts. The large cyst as well as smaller cystic dilatations of the ducts are visualized by means of colloidal thorium dioxide. They all communicate with the regional ducts.

Postmenopausal Involution.—Mrs. A. S., a housewife aged 52, had complained of severe mastalgia for the past three months. The tantalizing pains were confined to the outer lower quadrant of the left mammary gland and were associated with a spontaneous greenish white discharge from the nipple. There was no history of trauma, and the patient had not menstruated for the past eighteen months.

Both mammary glands were extremely small, atrophic and involuted. There was practically no parenchymatous tissue, but situated in the lower outer quadrant of the left breast was a tense neoplasm the size of a walnut. It was movable and semifluctuant and when compressed a tenacious greenish white fluid which contained degenerating leukocytes, epithelial cells and gram-positive diplococci escaped from the nipple. The breasts were so closely apposed to the wall of the chest that transillumination and soft tissue roentgenograms were very unsatisfactory.

A mammographic pattern was obtained by cannulating the lactiferous ducts and distending them with colloidal thorium dioxide. In the outer lower quadrant several regional ducts became confluent and formed a large cystic cavity (fig. 6). This cyst was able to evacuate its contents through its communicating ducts, which accounted for the escaping secretion. The remaining ducts honeycombed the matrix in a uniform manner, presenting a normal architectural pattern. In certain areas the ampullae were slightly dilated, and small localized cysts were formed.

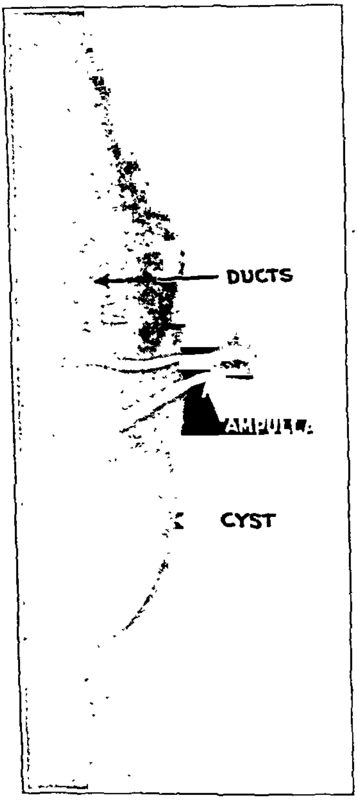

Fig. 6.—Mammogram in the case of an infected cyst. A large cyst which communicates with the ducts, thus accounting for the discharge, is visualized by means of colloidal thorium dioxide. The upper portion of the breast appears normal.

In this particular case the mammogram gave a clear concept of the disease process. The abnormal discharge originated within a small cyst and the involuting ducts. The mild secondary infection combined with the degenerative products of desquamation accounted for the characteristic greenish white color of the discharge. Radical therapy was not indicated, for such processes usually become quiescent after the menopausal balance has been established. The administration of thyro-ovarian extract and theelin and the application of moist heat usually suffice to control the immediate discomfort.

MILKY DISCHARGE

A milky discharge may occur in several conditions which prompt the patient to seek medical advice. Fortunately, a careful history and examination will usually divulge the pathogenic factors. Frequently such a discharge will seep from the nipples of the new-born, in which instance both breasts are hypertrophied, tense and tender. All symptoms subside spontaneously within two or three days. Occasionally a similar milky fluid escapes from virginal breasts during puberty. Postlactation involution is sometimes retarded, in which event there may be a spontaneous leakage of milk for several months after active nursing has subsided. Sometimes a small neoplasm is discovered in an actively secreting breast, and it becomes imperative to know whether it is a galactocele, an adenofibroma, a retention cyst or a carcinoma. Contrast mammograms are valuable in determining the exact status of the ducts and the secretory system.

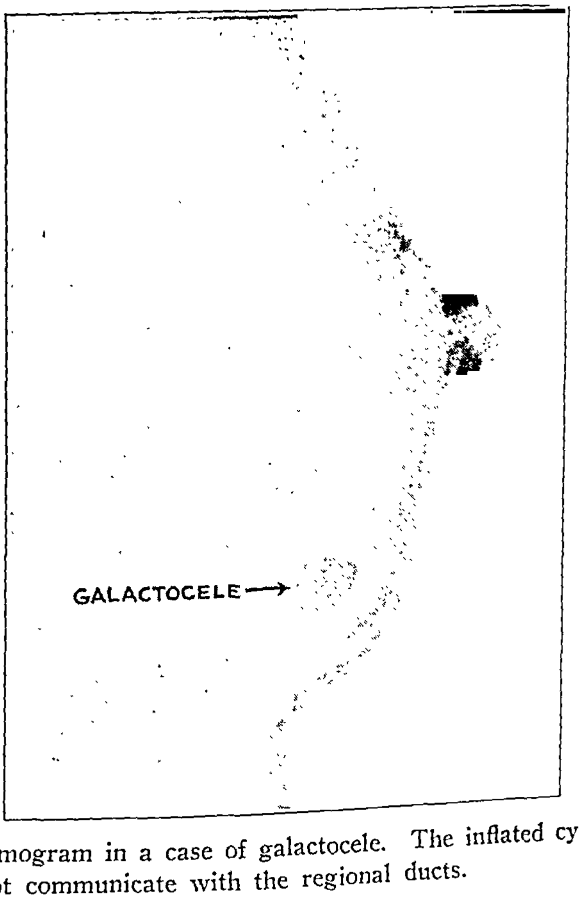

Fig. 7.—Mammogram in a case of galactocele. The inflated cyst has a smooth wall and does not communicate with the regional ducts.

Galactocele.—Mrs. A. M., a housewife aged 26, observed a painful "lump" in the lower part of the left breast about one month prior to the birth of her last baby, now 10 days old. On the third postpartum day, synchronous with the flow of milk, the mass more than quadrupled its size. Nursing or evacuation of the breast did not reduce the size of the intumescence.

A small encapsulated tumor the size of a walnut was palpable in the outer lower quadrant of the left breast. The neoplasm was not semifluctuant and did not transmit light. Milk could be expressed from several ducts, but no abnormal secretions were detected. Compression of the tumor did not augment the discharge or decrease the size of the mass.

In order to ascertain the exact nature of this midmammary neoplasm, an insufflation mammogram was made. An exploring needle was inserted directly into the tumor mass, 10 cc. of viscid milky secretion was aspirated and the cyst was distended with an equal volume of air. The walls of the inflated cyst were distinctly outlined, and there were no patent communications with the regional ducts (fig. 7). Such characteristics were pathognomonic of a sequestrated galactocele.

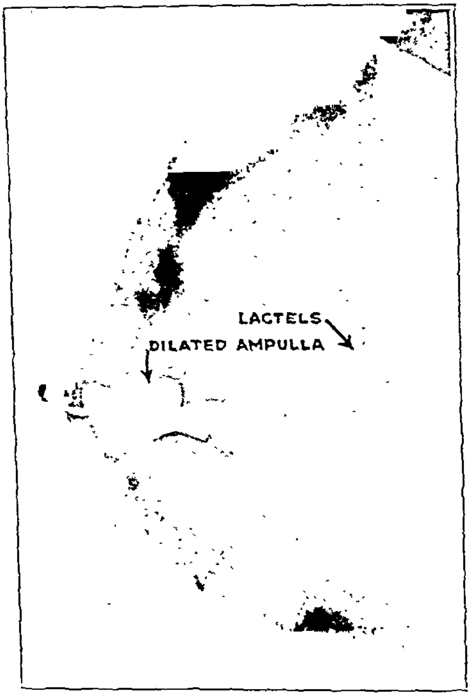

Fig. 8.—Mammogram of an engorged breast. There is enormous dilation of the ampulla and communicating ducts due to a retention of secretions.

In this particular case an accurate diagnosis was made without mutilating the lactating breast by taking biopsy specimens, and conservative treatment was instituted with no fear of causing undesirable complications.

Retention Engorgement of the Breast.—Mrs. R., a 26 year old housewife, entered the hospital complaining of "caked breasts." She had been well until two days prior to admission, at which time she decided to wean her 8 month old baby. In spite of the fact that she produced a copious supply of milk, she refused to nurse the child and would not permit the breasts to be decompressed by a pump. The mammary glands became large, swollen and very tender. A milky discharge seeped from the nipples, and for twelve hours she suffered excruciating pains, nausea, headaches and fever.

Both breasts were more than three times their regular size, and they were flushed, tense and exquisitely tender. Milk was escaping from several ducts of each nipple. The patient was very ill, with a temperature of 103.6 F. and a leukocyte count of 23,000.

It was apparent that the engorgement of her breasts was due to a retention of milk, but the intense pains, the febrile response and the leukocytosis suggested acute mastitis. An accurate visual concept of the disease process was obtained by mammographic studies. One of the seeping ducts was cannulated with a blunt no. 25 gage needle, but no thorium dioxide could be introduced without augmenting the intense pain. Apparently the ducts were so dilated with retained secretions that they were unable to accommodate the contrast fluid. A large quantity of viscid milk was aspirated from each breast by means of a pump, and both glands became soft and compressible. Fifteen cubic centimeters of colloidal thorium dioxide was injected into a centrally located duct in each breast. The mammographic silhouette demonstrated an enormously dilated ampulla and tributaries, but otherwise the pattern was normal (fig. 8). The intense mastalgia, the turgidity of the breast and the systemic responses were all caused by retention of normal secretions and not by a coincidental mastitis.

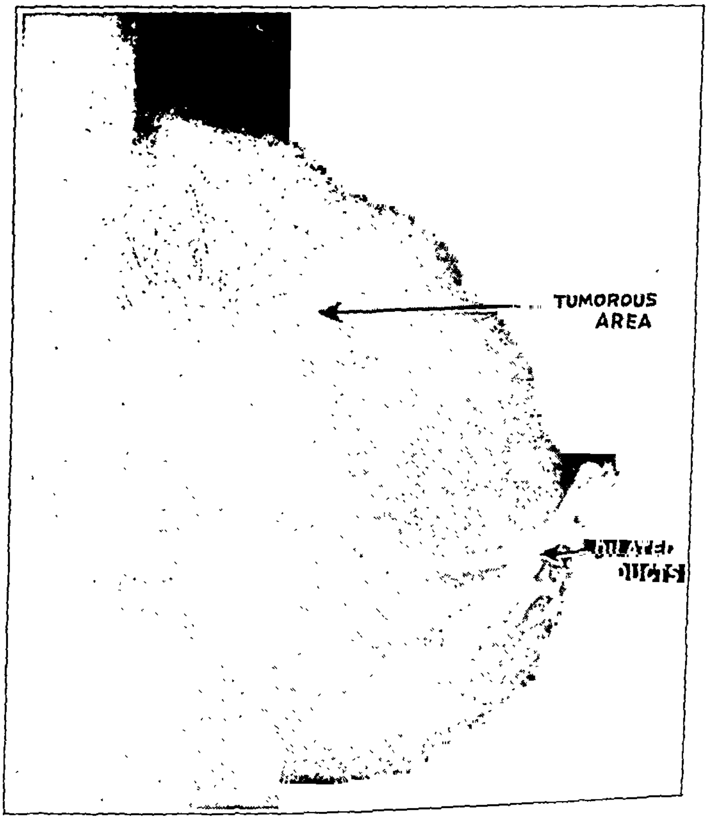

Fig. 9.—Mammogram in a case of "caked breast." The main duct is dilated, its walls are smooth and the communicating branches are large. In the tumorous area the ducts are small and compressed, but there is no evidence of localized invasion or destruction. The diagnosis was localized mastitis.

"Caked Breast."—Mrs. D., a 16 year old girl, gave birth to a baby who was sent to a foundlings' home. She never nursed the infant, and both breasts were permitted to undergo postpartum involution. During the first three days she complained of a mild mastalgia; from the fifth to the eighth day both breasts were swollen, engorged and painful; by the thirteenth day they were soft and pliable, except for one small indurated area in the upper outer quadrant of the left gland. Pressure on this tumor mass expressed a yellowish white material from one duct, while a clear milky secretion escaped from the others. In order to obtain a visual concept of the changes in the ducts, a mammogram was made.

Six cubic centimeters of colloidal thorium dioxide was injected into the duct which emitted the yellowish secretion, for it presumably drained both the tumorous and the normal portion of the breast. The segment of the visualized duct traversing the normal breast tissue appeared smooth and moderately dilated but otherwise normal, while the ramifying lacteal ducts which penetrated the indurated area were small, compressed and displaced (fig. 9). There was no evidence of destruction or invasion, which eliminated the possibility of a malignant process. The reduction in the size of the lacteal ducts was caused by a periductal inflammation and by retention of ductal secretions. The escaping yellowish discharge was composed of the products of inflammation and degenerating secretions which originated in the indurated or "caked" area.

COMMENT

A spontaneous emission of secretion from a nonlactating breast signifies an abnormal physiologic or pathologic condition. While such a symptom constitutes a definite warning, which should always be heeded, it must not be considered dangerous until so proved. Many unnecessary mastectomies have been performed for papillomas, serous cysts, galactoceles, postlactation involution, desquamative epithelial hyperplasia and chronic infections of the milk ducts just because such conditions provoked a discharge from the nipple. On the other hand, the dismissal of such symptoms as inconsequential may permit a benign lesion to undergo malignant transformation. Any physician, therefore, who assumes the responsibility of the management of lesions of the breast must be able to interpret the presenting signs and symptoms correctly. He cannot shift this diagnostic responsibility to the shoulders of the pathologist but must carry his own burden.

Contrast mammograms have proved invaluable in the recognition of mammary diseases. The true character of the offending lesion is clearly portrayed, and in addition the extent of the disease process is accurately determined. Such information is invaluable in aiding the surgeon to select the proper corrective procedure. If the mammogram demonstrates that the bloody discharge is being produced by a small isolated papilloma, excision of the tumor is curative. If, however, there are multiple papillomas, mastectomy is indicated. Likewise, if the stereomammogram demonstrates that the serous secretion originates from a simple cyst, conservative therapy may be employed, but if it reveals the presence of a carcinoma, radical measures are imperative.

The cases presented here were selected from a group in which three hundred and seventy-five mammographic studies were made. Experience indicates that the mammogram plays just as important a rôle in the diagnosis and treatment of lesions of the breast as does the pyelogram and the encephalogram in the recognition and treatment of disorders of the genito-urinary tract and the brain. Although the subject of mammography is still in its infancy, it holds forth promises of developing into an exact science. Additional experience and refinement of technic will add much to its value.

No mention has been made of the technic, indications and contraindications or complications after the injection of the ducts or insufflations of the breast, as these subjects have been treated adequately elsewhere.

SUMMARY

A spontaneous discharge from the nipple of a nonlactating breast is indicative of a physiologic or pathologic abnormality, but it furnishes no clue as to the provocative factor.

An abnormal discharge from the nipple means that the causative lesion has originated within or has secondarily invaded the ductal and secretory system of the breast.

A hemorrhagic, serosanguineous or serous discharge is not pathognomonic of any disease but may be associated with a papilloma, a carcinoma, a sarcoma or a simple cyst.

A serous, a greenish white, a purulent or a milky discharge may be symptomatic of desquamative epithelial hyperplasia, postlactation involution, "caked breast," retention mastitis, infection of the milk ducts, cysts or galactoceles.

A method of obtaining an accurate roentgenographic pattern of diseased or normal milk ducts has been developed. It consists of cannulating the orifices of the ducts with a blunt no. 26 gage needle and then distending them with contrast mediums, after which a stereoscopic roentgenogram is made. Any pathologic condition which destroys, invades, obstructs or distorts the ducts can be readily detected.

These visualizing mammograms are invaluable in determining the location, extent and identifying characteristics of pathologic states which produce abnormal discharge from the nipple. Typical mammograms demonstrating a papilloma, a carcinoma, a simple cyst, an infected cyst, retention mastitis, "caked breast," a galactocele and postlactation involution are presented.

The preoperative visualization of the breast permits an accurate diagnosis and the employment of the proper remedial measures. The need for biopsy and prophylactic mastectomy will be reduced to a minimum.

527 Medical Arts Building.

DOES OPERATIVE FUSION OF TUBERCULOUS JOINTS PRODUCE TUBERCULOUS MENINGITIS?

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Patients with tuberculosis of the joints often die of miliary tuberculosis, the most serious form of which is tuberculous meningitis. This is a problem that has long been troublesome to those who treat tuberculosis of the joints. Regardless of whether the patient is treated by conservative or by radical procedures, there is a certain mortality due to tuberculous meningitis. It is important, therefore, to attempt to determine which of the two phases of treatment of tuberculous joints allows the lowest mortality so far as tuberculous meningitis is concerned.

The records of the New York Orthopaedic Dispensary and Hospital lend themselves ideally to such a study because both the conservative and the radical treatment of tuberculosis of the joints have been given long trials at this institution.

For over forty years, or from the founding of the hospital in 1866 until 1911, tuberculosis of the joints was treated conservatively. A country hospital was opened in 1904 at White Plains, N. Y., where such patients could be treated by rest in bed, splints, casts and braces and where pure air, sunshine and good food were available.

The era of so-called radical treatment, of operative procedures for the purpose of eliminating all motion in tuberculous joints, had its inception at this hospital on Jan. 9, 1911. At that time, the first operative fusion for tuberculosis was performed by Dr. Russell A. Hibbs, for tuberculosis of the second and third lumbar vertebrae in a boy 9 years old. And for the twenty-five years since that time, operative fusion for all joints affected by the tubercle bacillus has been carried out in this institution. A comparative study, therefore, of the incidence of tuberculous meningitis following conservative treatment of tuberculosis of the joints with that following operative treatment can be made.

Disagreement exists as to whether operation on a tuberculous joint will or will not disseminate the disease and produce tuberculous meningitis. Many surgeons who definitely believe that fusion of tuberculous joints cures the tuberculosis state that the risk of producing meningitis thereby forces them to treat conservatively all patients with tuberculous joints. This factor alone seems to have cast certain disrepute on operative fusion of joints for tuberculosis, especially when children are involved.

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1. Does surgical intervention, therefore, produce tuberculous meningitis?

2. Does fusion of tuberculous joints decrease the mortality due to tuberculous meningitis?

With these questions in mind, the deaths due to tuberculous meningitis prior to the advent of operative fusion were investigated, recorded and compared with such fatalities since operative fusion was instituted. The date selected as the dividing line was 1912, since this was near the middle of the period during which the conservative treatment of tuberculosis of the joints was discontinued at the New York Orthopaedic Dispensary and Hospital. Therefore, the time from 1912 to 1935 was considered as the period of operative treatment of tuberculosis of the joints as against an equivalent length of time, from 1889 to 1912, which was designated as the period of conservative treatment.

TABLE 1.—*Incidence of Tuberculous Meningitis Before and After Operative Treatment of Tuberculosis of the Joints*

	1889-1912	1912-1935
No. of patients with tuberculosis admitted to the hospital	1,398	1,752
No. of operations, other than aspiration, performed on tuberculous patients	0	1,941
No. of deaths due to tuberculous meningitis	149	23
Percentage of deaths due to tuberculous meningitis in patients with tuberculosis	10.6	1.3

During the twenty-three year period before operative fusions came into use, when all tuberculous patients were treated conservatively, 1,398 persons with tuberculosis were admitted to the hospital, on whom no operations other than aspiration were performed. However, 149, or 10.6 per cent, of these patients died of tuberculous meningitis, making an average of 6½ deaths per year.

During a similar length of time when operative fusion was performed, there were 1,752 patients with tuberculosis admitted to the hospital, on whom 1,941 operations were performed. Only 23 of these patients, however, died of tuberculous meningitis. This is a percentage of 1.3 for patients admitted and 1.1 for operations performed, with an average of 1 death per year.

It should be stated here that 8 of the 23 deaths occurring between 1912 and 1935 were of patients on whom no operations had been performed because of their delicate condition at the time of admittance and during their stay in the hospital. If these 8 deaths were eliminated because of the fact that the patients were not operated on, the percentage of deaths for those patients who were operated on would drop from 1.1 to 0.77.

In all the 23 fatal cases, tuberculosis had been present in some form for from six months to seventeen years prior to the onset of tuberculous meningitis. The period that had elapsed between the date of operation and the onset of meningeal symptoms in the 15 patients who were operated on is given in table 2.

After studying table 2, it is difficult to state which deaths, if any, were directly due to operation. Each patient presented the true signs and symptoms of tuberculous meningitis, and none died of postoperative shock or other conditions extraneous to this discussion. The period necessary for tuberculous meningitis to develop and proceed to death is extremely variable. The duration of development is not known. It must be very inconstant if it parallels the length of time before death occurs after meningeal symptoms become evident, because death ensues rapidly in some patients, while others show a slow, steady decline after the appearance of the first sign of meningeal irritation.

Table 2.—*Length of Time from Operation to Onset of Meningeal Symptoms*

Length of Time	No. of Cases	Length of Time	No. of Cases
4, 9 and 10 days	3	5 months	2
4 weeks	2	8 months	3
6 weeks	1	[illegible]	1
9 weeks	1	[illegible]	1
4 months	1	No operations performed	8

Table 3.—*Postmortem Status of the Involved Joints*

No. of Cases	Status of Case	Status of Joint
1	Spinal fusion	Grossly solid
1	Spinal fusion	Definitely not solid
1	Sacro-iliac fusion	Definitely not solid
2	Tuberculosis of spine and hip associated	Spinal fusion solid; hip not operated on
4	No autopsy	Presence of fusion not known
6	Early death	Too early for fusion
8	No operation	No fusion

Postmortem examinations were made on all but 4 of the 15 patients operated on. The diagnosis of tuberculous meningitis was confirmed in each case. Also a careful examination was made for the presence or absence of fusion. In only 1 patient was the fusion definitely solid—a patient with tuberculosis of the spine. In 2 patients a spinal fusion and a sacro-iliac fusion, respectively, were definitely not solid. In 2 patients who presented tuberculosis of the spine associated with tuberculosis of the hip, the spinal fusions were grossly solid; the hips were not operated on. Death occurred too early for fusion to have taken place in 6 patients. The status of the joint was not known for 4 patients on whom autopsy was not allowed, and it is obvious that fusion was not present in the 8 patients who had not been operated on.

In summary, in 1 case the fusion was solid, in 4 the status of the joint was not known and in 18 fusion was not present. This, therefore, is evidence that lack of either operative or natural fusion of a tuberculous joint is in many cases a predisposing factor to tuberculous meningitis.

COMMENT

There might be criticism from several standpoints of the statistics presented herein. It might be said, for instance, that the diagnoses may not have been as accurate in the nineties as they are today, i. e., that perhaps tuberculous meningitis was not always diagnosed or was diagnosed erroneously. But from such reasoning it might be said, also, that perhaps tuberculosis of the joints was not always diagnosed accurately either. "Hip joint disease" treated as tuberculosis may not have been tuberculosis, for were not many of these cases in which cure was effected in that period really cases of coxa plana, slipping of the upper epiphysis of the femur and other conditions not caused by acid-fast bacilli. Osteomyelitis of the spine was rarely, if ever, differentiated from tuberculosis of the spine. In cases of the former tuberculous meningitis naturally would not be expected to develop, yet the condition might have been considered tuberculosis of the joints. Therefore, if the diagnoses were more inaccurate in the nineties than they are today, the error may favor equally the two sides of the question of tuberculous meningitis following tuberculosis of the joints.

It should be noted, however, that the patients treated during the conservative era were hospitalized for a longer period than those treated by operation, because the time required for treatment of tuberculosis of the joints is much greater when such joints are treated wholly by rest than when they are treated by operative fusion. The point might be raised, therefore, that the incidence of tuberculous meningitis would be greater in hospitalized patients observed for a long period than in those observed for a shorter period, because there would be more time during which tuberculous meningitis might develop. This factor being admitted, it would be fair to assume that the mortality percentage would be decreased no more than one-half. The figures then would be 5.3 per cent deaths instead of 10.6 per cent in patients not operated on, as opposed to about 1 per cent in patients operated on. However, this would still leave the mortality rate five times greater for nonoperative treatment than for operative treatment.

In fact, even if one carries the point so far as to consider the number of deaths as being equal for each twenty-three year period, there still is no evidence for the theory that to operate on a tuberculous joint incites tuberculous meningitis.

The answer, therefore, to the questions asked earlier seems to be: (1) that surgical intervention in a tuberculous joint does not produce tuberculous meningitis and (2) that fusion of tuberculous joints definitely decreases the mortality due to tuberculous meningitis.

CLINICAL AND EXPERIMENTAL OPERATIONS ON THE GALLBLADDER AND COMMON DUCT

RESULTS OF PRIMARY SUTURE

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Further progress in surgery of the biliary tract must depend on a reduction in mortality and morbidity, on a reasonable certainty of obtaining relief with a preservation of the maximum function and on a simplified technic, and must lead to earlier operation.

The first operation on the gallbladder has been credited to Fabricius,[1] who removed gallstones in 1618. Hulke[2] referred to a case reported about 1706 in which a stone was withdrawn from the gallbladder by a forceps. Petit[3] in 1743 reported a case in which stones were removed from a gallbladder which was incised when it was mistaken for an abscess, and the patient recovered. Thudichum[4] in 1859 proposed the removal of stones by drainage in two stages.

The first operation on the gallbladder in one stage was performed in 1867 by Bobbs[5] when he removed many gallstones and closed the incision by primary suture. The patient had occasional attacks of distress due to an overlooked stone in the cystic duct, but otherwise he had good health for over thirty-two years.

Early in 1878 Brown[6] explored a distended gallbladder without opening it. Spontaneous rupture and biliary drainage followed the freeing of adhesions, and the patient recovered.

Presented before the Chicago Surgical Society, March 6, 1936.

[1] Fabricius, 1618, quoted by Tucker, M. T.: Bull. Johns Hopkins Hosp. **12**:249, 1901.

[2] Hulke, in discussion on Bryant.[10]

[3] Petit, 1743, cited by Power, D'Arcy: Gallstones: A Plea for Earlier Operation, Brit. J. Surg. **1**:21, 1913.

[4] Thudichum, J. L.: On the Pathology and Treatment of Gall Stones, Lancet **2**:421, 1859; cited by Brown.[6]

[5] Bobbs, John S.: Case of Lithotomy of the Gall-Bladder, Tr. Indiana M. Soc. **18**:68, 1868. Brayton, A. W.: John S. Bobbs, of Indianapolis, the Father of Cholecystotomy, Indiana M. J. **24**:20 (July) 1905.

[6] Brown, George: On the Treatment of Dropsy of the Gallbladder by Operation with Notes of a Successful Case, Brit. M. J. **2**:916 (Dec. 21) 1878.

Kocher[7] performed the first successful drainage of the gallbladder in June 1878. Sims[8] and Keen[9] shortly afterward drained the gallbladder, but their patients died. In 1879 Bryant[10] and Tait[11] reported successful drainage operations. The first successful cholecystectomy was performed by Langenbuch[12] on July 15, 1882.

Cholecystotomy with primary suture was used by Meredith[13] in 1883. This method was advocated by Rutherford Morison[14] when the gallbladder appeared to be in good condition, without infection or obstruction of the ducts by stones, and was used by many surgeons with good results.[15] However, Robson reported a fatal bile leak, and Kocher observed occasional recurrence of gallstones. Courvoisier,[16] Kocher and others at first anchored the sutured gallbladder to the abdominal wall, and a few sutured the wound extraperitoneally (Brockbank[17]).

Unfortunately, in this pioneer period primary suture was used by Deaver and others[18] in cases in which the cystic duct was obstructed and in acute and chronic conditions in which either drainage or removal of the gallbladder should have been done.

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[7] Kocher, cited by Judd, E. S.; McIndoe, and Marshall, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1934, vol. 7.

[8] Sims, Marion: Cholecystotomy in Dropsy of the Gallbladder, Brit. M. J. **1**:811 (June 8) 1878.

[9] Keen, W. W.: A Case of Cholecystotomy, with Remarks, Am. J. M. Sc. **77**:134 (Jan.) 1878.

[10] Bryant, T.: A Case in Which a Biliary Calculus Was Removed by Operation from the Gallbladder, Brit. M. J. **1**:819 (May 31) 1879.

[11] Tait, Lawson: Cholecystotomy Performed for Dropsy of the Gallbladder Due to Impaction of a Gallstone, Brit. M. J. **2**:778 (Nov. 15) 1879.

[12] Langenbuch, C.: Ein Fall von Exstirpation der Gallenblase wegen chronischer Cholelithiasis, Berl. klin. Wchnschr. **19**:725, 1882.

[13] Meredith, cited by Moynihan, B. G. A.: Abdominal Operations, Philadelphia, W. B. Saunders Company, 1915, vol. 2, p. 275.

[14] Morison, Rutherford: Surgical Contributions from 1881 to 1916, Baltimore, William Wood & Company, 1916, vol. 2.

[15] Marcy, H. O., in discussion on Richardson, M. H.: The Importance of Early Operation in Gall-Stones, J. A. M. A. **35**:1397 (Dec. 1) 1900. Pick, T. P.: A Case of Cholecystotomy, Internat. Clin. **3**:188, 1895. Meyer, W.: Ideal Cholecystotomy (Koenig's Incision), Ann. Surg. **58**:694, 1913. Robson, A. W. Mayo: Diseases of Gallbladder and Bile Ducts, ed. 3, Baltimore, William Wood & Company, 1904; Two Successful Cases of Cholecystotomy, with Results, Brit. M. J. **2**:833 (Oct. 31) 1885. Wells, Spencer, cited by DaCosta, J. C.: Modern Surgery, ed. 9, Philadelphia, W. B. Saunders Company, 1925, p. 1110. Kocher, quoted by Bickham, W. S.: Operative Surgery, Philadelphia, W. B. Saunders Company, 1924, vol. 4, p. 508.

[16] Courvoisier, cited by Bickham, W. S.: Operative Surgery, Philadelphia. W. B. Saunders Company, 1924, vol. 4, p. 508.

[17] Brockbank, E. M.: On Gallstones or Cholelithiasis, Philadelphia, P. Blakiston's Son & Co., 1896.

[18] Deaver, J. B.: Cases of Cholecystotomy, Ann. Surg. **44**:61, 1896. Musser, J. H., and Keen, W. W.: Cholecystotomy, Am. J. M. Sc. **88**:333 (Oct.) 1884.

The two stage operation in which the gallbladder was first sutured to the abdominal wall and later drained was tried by Halsted[19] and others, who promptly abandoned it for the single stage drainage operation. At first the drained gallbladder was sutured to the abdominal wall (Tait), but biliary fistula resulted frequently; the results were much better when it was not fixed to the wound (Robson).

Drainage of the gallbladder rapidly became the procedure of choice,[20] because most of the patients coming to operation had extensive changes in the biliary tract or liver with infection or jaundice. In recent years, owing to the increase in the frequency of operations for chronic conditions, the disadvantages of a biliary fistula (Ravdin[21]) and the large number of secondary operations after drainage, cholecystectomy has become the usual operation of choice (Palmer[22] and Bunts[23]).

Lack of roentgenographic visualization as a final test of function rather than pathologic changes in the liver and gallbladder have become only too frequently the indication for routine removal of the gallbladder. With slight alterations in the gallbladder and even after drainage or anastomosis, diminished visualization gives no final index of later function nor a true index of present tonus, elastic recoil (Copher, Kodama and Graham[24]) or contractile power (Ivy[25]).

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19. Halsted, cited by Bloodgood, J. C.: Halsted Thirty-Six Years Ago, Am. J. Surg. **14**:89 (Oct.) 1931.

20. Ochsner, A. J.: Technique of Gall-Bladder Operations, Surg., Gynec. & Obst. **2**:204 (Feb.) 1906. Moynihan, B. G. A.: Abdominal Operations, Philadelphia, W. B. Saunders Company, 1914, vol. 2, p. 275. Mayo, W. J.: The Present Status of Surgery of the Gallbladder and Bile Ducts, M. Rec. **63**:289 (Feb. 21) 1903; Surgery of the Gallbladder, Illinois M. J. **49**:303 (April) 1926; "Innocent" Gall-Stones a Myth, J. A. M. A. **56**:1021 (April 8) 1911. DaCosta, J. C.: Modern Surgery, ed. 9, Philadelphia, W. B. Saunders Company, 1925, p. 1034. Means, W. J., in discussion on Richardson, M. H.: The Importance of Early Operation in Gall-Stones, J. A. M. A. **35**:1397 (Dec. 1) 1900. Cheeseman, W. S.: Cholecystotomy, M. Rec. **44**:225 (Aug. 19) 1893.

21. Ravdin, I. S.: Drainage of Common Duct, S. Clin. North America **14**:127 (Feb.) 1934. Ravdin, I. S.; Riegel, C.; Johnston, C. G., and Morrison, P. J.: Studies in Biliary Tract Disease, J. A. M. A. **103**:1504 (Nov. 17) 1934.

22. Palmer, D. W.: The Rationale of Gallbladder Therapeusis, Ohio State M. J. **21**:309 (May) 1925.

23. Bunts, F. E.: Diagnosis and Surgical Treatment of Diseases of the Gall-Bladder, Ann. Surg. **82**:232 (Aug.) 1925.

24. Copher, G. H.; Kodama, S., and Graham, E. A.: Filling and Emptying of the Gall Bladder, J. Exper. Med. **44**:65 (July) 1926.

25. Ivy, A. C.: The Physiology of the Gall Bladder, Physiol. Rev. **14**:1 (Jan.) 1934.

The inflamed gallbladder may be visualized partially or not at all (Ivy and Bergh[26]), but whether the inflammation is primary or secondary to hepatitis cannot be demonstrated by a functional test. Clinical evidence has shown that this function may return after acute cholecystitis (Murphy and Bollman[27]). Ravdin and his co-workers found that bile salts could be completely absorbed from a damaged gallbladder.

Eusterman[28] pointed out that in about 10 per cent of cases the normal gallbladder gives a pathologic response, that is, a faint shadow or invisibility, which may be due to errors both in technic and in interpretation. He found a large group of cases in which there was positive cholecystograhpic evidence of disease but insufficient clinical symptoms or an absence of them.

Schmechel[29] reported relief after cholecystectomy in only 23.4 per cent of sixty patients in the absence of stones, while Graham and Mackey[30] observed relief in 60 per cent.

In routine removal of the gallbladder, especially in acute conditions, Stone and Owings[31] disregarded the greater safety of drainage, the possibility of a return of function and some of the well established technical and late complications of cholecystectomy. Several months after experimental cholecystectomy Ivy[25] observed the development of hepatitis. The dangers of ascending infection from an incompetent sphincter or from the formation of stones in the common duct may counterbalance the benefits of cholecystectomy.

Crump[32] found gallstones in 32.5 per cent of a thousand gallbladders at necropsy and cholesterosis in 36.8 per cent, making a total of 76.1 per cent of gallbladders with pathologic changes. There were stones in the ducts in 24 per cent, of which 60.2 per cent were at the papilla and 48.7 per cent in the cystic duct.

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[26] Ivy, A. C., and Bergh, G. S.: The Applied Physiology of the Extrahepatic Biliary Tract, J. A. M. A. **103**:1500 (Nov. 17) 1934.

[27] Murphy, G. T., and Bollman, J. L.: Concentrating Activity of Bile in Gallbladder Following Restoration from Acute Experimental Cholecystitis, S. Clin. North America **11**:917 (Aug.) 1931.

[28] Eusterman, G. B.: Cholecystography: A Clinical Appraisal, Proc. Staff Meet., Mayo Clin. **2**:138 (June 22) 1927.

[29] Schmechel, A.: Spätresultate operierter steinfreier Gallenblasen (Cholecystitis sine concremento), Zentralbl. f. Chir. **61**:673 (March 24) 1934.

[30] Graham, E. A., and Mackey, W. A.: Consideration of Stoneless Gallbladder, J. A. M. A. **103**:1497 (Nov. 17) 1934.

[31] Stone, H. B., and Owings, J. C.: The Acute Gallbladder as a Surgical Emergency, Ann. Surg. **98**:760 (Oct.) 1933.

[32] Crump, C.: The Incidence of Gall Stones and Gall-Bladder Disease, Surg., Gynec. & Obst. **53**:447 (Oct.) 1931.

Drainage of the gallbladder has permitted the recovery of critically ill patients, frequently with a return of function. Halsted, Dieterich[33] and others observed that few of the badly damaged gallbladders which were drained gave rise to symptoms later, and only a few were reoperated on for stone in the common duct.

Chronic diseases of the heart, liver and kidney may become aggravated when cholecystectomy is done, and occasionally unexplained death follows. When function of the gallbladder exists, a sudden hepatic disturbance without previous compensatory changes may follow cholecystectomy (Cantarow, Gartman and Ricchiuti[34]).

The symptoms of disease of the gallbladder may be aggravated or actually begin (Case[35]) after an operation for drainage when normal or partial function is lost.

Rose[36] found on visualization of a series of gallbladders that of 801 with pathologic conditions 101 had normal function with stones, 161 poor function with stones, 209 faint filling, 90 delayed filling or emptying and only 240, or 30 per cent, no filling.

The function of the gallbladder after drainage has been carefully studied by visualization tests. In a series of twenty cases in which cholecystograms were made after cholecystostomy, Case found the gallbladder to be normal in three, while in eight there was a delayed or insufficient response, largely the result of adhesions, in seven stones were found and in two there was obstruction of the cystic duct. These findings were confirmed by reoperation.

Saint[37] found that the function of the gallbladder after drainage was impaired in eighteen cases, lost in eleven and good in seven. He reviewed the findings of others and concluded that drainage of the diseased gallbladder with the hope of a return of function was futile. He stated that he preferred removal in both acute and chronic conditions.

In recent years occasional reports by Willis,[38] Saint[37] and Sutherland[39] corroborate the merits of primary suture of the gallbladder after cholecystotomy in certain conditions.

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[33] Dieterich, H.: Ergebnisse nach Cholecystostomie, Chirurg **5**:929 (Dec. 15) 1933.

[34] Cantarow, A.; Gartman, E., and Ricchiuti, G.: Hepatic Function: Effect of Cholecystectomy on Hepatic Function, Arch. Surg. **30**:865 (May) 1935.

[35] Case, J. T.: Personal communication to the author, Sept. 23, 1935.

[36] Rose, C. B.: Cholecystography, S. Clin. North America **12**:1083 (Oct.) 1932.

[37] Saint, J. H.: Late Results of Operations on Biliary Tract in Three Hundred Fifty-Nine Cases, Brit. J. Surg. **23**:299 (Oct.) 1935.

[38] Willis, A. M.: Ideal Cholecystotomy, J. A. M. A. **78**:942 (April 1) 1922.

[39] Sutherland, C. G., in discussion on Weir, J. F., and Snell, A. M.: Symptoms That Persist After Cholecystectomy, J. A. M. A. **105**:1093 (Oct. 5) 1935.

Restoration or preservation of the function of the gallbladder by primary suture has not been reported previously. The current belief is that function will be entirely lost, and the operation is never performed for the purpose of restoration (Judd and his co-workers[40]).

It is my belief that elderly patients or those who are poor risks will have less postoperative reaction with fewer hepatic and pulmonary complications and much better function after primary suture with cholecystotomy than after either drainage or removal. Improvement in cardiac condition has been noted clinically with a definite return toward normal after operations on the gallbladder (Fitz-Hugh and Wolferth[41]).

EXPERIMENTAL DATA

A series of experiments on dogs was planned to determine the early and late changes occurring in the gallbladder, bile ducts and liver. In all experiments primary closure of the abdomen was performed.

RESULTS OF INCISION OF GALLBLADDER WITH LIGATION OF CYSTIC DUCT

In nineteen experiments the gallbladder was split wide open from the fundus to the cystic duct with ligation of the cystic duct. In some of the experiments the cystic duct was permanently ligated with linen, while in others it was ligated with catgut, which usually permits the duct to open after from ten to fourteen days unless unnecessary trauma or heavy suture material is used.

In eleven of the experiments occlusion of the cystic duct was noted at postmortem examination. In six of these experiments, of from thirty-six to one hundred and fifteen days' duration, the cystic duct was ligated with linen and the gallbladder was split and left open. In five the cystic duct was ligated with catgut; in two there was obstruction on termination at the end of one week, while in three permanent occlusion resulted after from one to five months.

In two experiments after one week of occlusion of the cystic duct the gallbladder had reformed, except for a small area which was sealed by adhesions to the liver. In one experiment the gallbladder contained precipitated bile pigment with mucus.

In nine experiments in which there was occlusion of the cystic duct for from one to five months the gallbladder had entirely healed, and in two it was practically normal in size with a thin wall. In two experiments the gallbladder was enlarged; in one of these it had a thin wall and contained clear mucus with particles of bile pigment, and in the other it had an empyema with several small abscesses in the adjacent liver. In four experiments the gallbladder was contracted to from one-half to two-thirds its normal size. In the lumen of one gallbladder there was only thick mucus; in the lumen of two others a mass like coagulated mucus was found after one and five months, respectively, with bile stain in one, and in the lumen of the fourth gallbladder there was mucus with a gritty precipitate of bile. In one experiment the gallbladder was only about 1 cm. in diameter and contained a mass of laminated bile pigments with tarry bile and mucus.

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[40] Judd, E. S.; McIndoe and Marshall, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1934, vol. 7.

[41] Fitz-Hugh, T., and Wolferth, C. C.: Cardiac Improvement Following Gall-Bladder Surgery: Electro-Cardiographic Evidence in Cases with Associated Myocardial Disease, Ann. Surg. **101**:478 (Jan.) 1935.

There was bile pigment in five of the eleven gallbladders examined, or 45 per cent, although bile was removed and the cystic duct ligated completely in from one to fifteen weeks. In the experiments in which the cystic ducts were permanently obstructed no sand or precipitated bile was found in the common duct, although the duct was dilated in seven of the nine experiments which lasted over one week.

There were seven experiments of from one week to over four months' duration in which the gallbladder was split completely and the cystic duct was temporarily occluded by a catgut ligature. The catgut was absorbed in approximately from ten to fourteen days, with no stricture or scarring. In one experiment it was absorbed before the split gallbladder was closed, and when the acutely ill animal was killed after six days the gallbladder was found to be covered with a thick precipitate of bile, to show bile peritonitis but to contain no pus. In two other experiments precipitated bile pigment was found in the gallbladders. In one experiment (no. 74) bile sand was found in the gallbladder and the common duct after two weeks, and in another (no. 62) it was found only in the duct. Precipitated bile pigment was found in the gallbladders of 60 per cent of the animals in this group and somewhere in the biliary tract of 71 per cent.

The common duct was normal in four experiments and enlarged in three, with bile pigment in two, or 30 per cent.

RESULTS OF INTRAVENOUS INJECTION OF DYE

In five experiments sections of the gallbladder were examined after the intravenous injection into the dogs of from 0.08 to 0.25 Gm. of tetrabromophenolphthalein sodium per kilogram of body weight. In two experiments the gallbladder showed slight edema and increased round cell infiltration after from one to two weeks, but in two which were extended over three and six months the gallbladders were normal except for slight adhesions at the fundus where sections had been removed.

In seven experiments, after the intravenous injection of from 0.04 to 0.05 Gm. of tetraiodophenolphthalein per kilogram of body weight, sections of the gallbladder showed little or no change after one week. However, a few gross particles of bile pigments were found in the bile from the gallbladder in two experiments, and in a third (no. 53) a large amount of so-called sand was found at the end of one week, although no operation had been done on the gallbladder or abdomen. In a fourth experiment (no. 31), after a large piece of the gallbladder was removed for microscopic examination at the end of one week, the animal was permitted to live eight months. The gallbladder was about two-thirds normal size and largely functionless but contained no bile sand, while the common duct was considerably dilated and thickened and contained a large amount of bile pigment. The liver appeared to be normal. This makes precipitated bile pigment in the gallbladder in three, or 43 per cent of the experiments, one week after the intravenous injection of dye.

In about one third of these twelve experiments occasional areas of focal necrosis were found in the liver which contained polymorphonuclears, lymphocytes and a few fibroblasts. Sections taken several weeks later and also from numerous control animals did not show these changes.

One week after the intravenous injection of 0.04 or 0.05 Gm. of tetraiodophenolphthalein per kilogram of body weight into fourteen rabbits there were no changes in the gallbladder and liver.

Graham, Cole, Copher and Moore[42] concluded that the toxicity of this halogenated dye group was due to the phenolphthalein part of the molecule.

Acute degeneration of the liver in a patient after the giving of the dye clinically was reported by Dyas, Sheldon and Dyke.[43] A serious reaction was observed by Bailey[44] in a patient with jaundice. Visualization of the gallbladder should not be attempted during attacks of obstruction of the biliary tract, acute hepatitis or cholecystitis or after any period of starvation or illness.

The effect on the gallbladder of direct injection of varying concentrations of tetrabromophenolphthalein sodium was observed in seven experiments.

After intravenous injection, Copher observed that there was an average concentration of 0.2 per cent of bromine in the bile from the liver, while there was 0.6 per cent in that from the gallbladder, which did not excrete or absorb the dye to any extent.

RESULTS OF DIRECT INJECTION OF SOLUTIONS INTO THE GALLBLADDER AND COMMON DUCT

In two experiments 10 cc. of a 12.5 per cent solution of tetrabromophenolphthalein sodium was injected into the gallbladder without ligation of the cystic duct. There were edema and increased round cell infiltration one week later. After one hundred and fifty days there was no change except a slight adhesion at the site of the injection.

In three experiments a 12.5 per cent solution of tetrabromophenolphthalein sodium was injected into the gallbladder with ligation of the cystic duct with linen. After seven days there was marked distention with acute inflammation and necrosis of the wall of the gallbladder with turbid contents. Microscopically, there were edema, hemorrhagic areas, many round cells and extensive desquamation of the epithelium and definite hepatitis.

In another experiment after seventy-five days there was a nubbin gallbladder, 1 cm. in diameter, which contained a small mass of soft bile pigment and mucus, with marked fibrosis and an absence of epithelium.

In one experiment acute inflammation was found one week after injection of a 5 per cent solution of the dye into the gallbladder with ligation of the duct. Roentgenograms made after from three to seven days showed some absorption of the dye by the gallbladder.

In six experiments a 15 per cent solution of sodium iodide was injected into the gallbladder without ligation of the cystic duct. Four of these experiments were terminated in from four to eight days. In one the gallbladder was surrounded by adhesions and was somewhat contracted. There were edema and a slight increase in the round cells. The liver was normal. In two experiments at the end of one hundred and sixteen and one hundred and nineteen days there were only slight adhesions about the site of injection, while cultures and sections from the gallbladder and liver were negative.

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[42] Graham, E. A.; Cole, W. W.; Copher, J. H., and Moore, S.: Cholecystography: The Use of Phenoltetraiodophthalein, J. A. M. A. **86**:1899 (June 19) 1926.

[43] Dyas, G. E.; Sheldon, J. H., and Dyke, S. C.: Death Coincident with Oral Administration of Sodium Tetraiodophenolphthalein, Brit. J. Radiol. **1**:75 (March) 1928.

[44] Bailey, Hamilton: Emergency Surgery, ed. 2, Baltimore, William Wood & Company, 1936, p. 139.

In one experiment two hundred and forty days after the injection of a 15 per cent solution of sodium iodide into the gallbladder with ligation of the cystic duct with linen there was marked contraction and fibrosis of the gallbladder to 1 cm. in diameter. It contained a small ball of mucus with some bile pigment. There was apparent progressive obliteration of the lumen nearly to the fundus. The common duct was moderately enlarged. The fibrotic changes were similar to those seen after the injection of a 12.5 per cent solution of tetrabromophenolphthalein sodium.

In two experiments a 15 per cent solution of sodium bromide was injected into the gallbladder without obstruction. After six days there were edema of the wall and a precipitated mass of bile pigment around the puncture wound. In one experiment no change was observed after ninety-five days.

In one experiment a 15 per cent solution of thorium nitrate was injected into the gallbladder without obstruction. After six days there were edema, increased round cell infiltration and a few polymorphonuclear cells. There was some congestion of the liver.

In one experiment physiologic solution of sodium chloride was injected into the gallbladder as a control, with no changes except a few adhesions at the site of injection after twenty days.

In many of the experiments cultures of the bile and liver were taken and found to be negative.

In thirteen experiments various solutions were injected into the gallbladder without ligation of the cystic duct. A deposit of pigment was found in only one gallbladder; this occurred at the site of the injection.

In six experiments the cystic duct was ligated permanently at the time of injection of the dye or sodium iodide into the gallbladder. Pigment was found in the gallbladder in two. There was no bile sand in the common duct in these nineteen experiments.

Some chemical inflammation of the gallbladder resulted, especially from the dye and the solutions of sodium bromide and thorium when the cystic duct was not ligated, but it quickly cleared. There was some congestion in the liver at the end of a week.

The cystic duct was ligated in three control experiments:

In one the cystic artery and duct were ligated with linen, and the neck of the gallbladder was crushed. One week later the gallbladder was moderately distended but was of a normal color. Microscopically, only slight changes were observed.

In one experiment seventy-five days after ligation of the cystic duct with linen the gallbladder was contracted to one-third normal size and contained thick mucus but no bile. There was moderate fibrosis of the wall. The cystic duct was dilated below the ligature. Cultures were negative.

In another experiment the cystic duct was ligated with plain catgut so that it would remain obstructed for only about ten days. After forty-nine days the gallbladder and the liver were normal with a patent cystic duct.

In one experiment the common duct was ligated, and 12 cc. of a 15 per cent solution of sodium iodide was injected into the gallbladder. Death occurred in three days. There were extensive icterus and evidence of a septic cholangeitis, with positive cultures. The gallbladder was filled with black concentrated bile with little gross change, although the ducts were dilated.

In a control experiment the common duct was cut and ligated. After five days the animal was in good condition with no evident icterus, but the gallbladder was distended and filled with thick mushy bile. There was hyperplasia of the mucosa, and cultures of the gallbladder and liver were negative.

In one experiment the insertion of a small needle into a normal gallbladder for injection resulted in a leak, with fatal bile peritonitis. After this the site of the puncture was ligated with catgut, because silk was observed to cut through into the lumen of the gallbladder.

SUMMARY OF DATA

In most experiments in which a small section was removed from the fundus of the gallbladder for microscopic examination there were few adhesions. Occasionally after a large section was removed contraction and a dilated common duct resulted, indicating a functionless gallbladder.

In three, or 5.1 per cent, of the fifty-four experiments on dogs, bile pigment sand or crystals were present in the common duct: In experiment 74, after the gallbladder was split and temporary occlusion of the cystic duct produced, the experiment being terminated after fourteen days, there were masses of pigment in both the gallbladder and the common duct. In experiment 62, which was similar to experiment 74, the gallbladder was adherent, and there was bile sand in the common duct after four and one-half months. In experiment 31 the injection of dye intravenously was followed by the removal of a large section from a normal gallbladder eight months previously, and at necropsy the gallbladder was contracted moderately with normal bile, but the common duct was dilated and contained a large amount of black sand. Previously, I[45] reported gallstones in the common duct after experimental suture of the common duct.

In nineteen experiments, after permanent obstruction of the cystic duct by ligature and removal of all bile, some bile pigment was found in seven gallbladders, or 36 per cent. This could enter only through small anastomosing bile ducts to the liver or by secretion.

Several months after the injection of a concentrated solution of sodium iodide and dye with ligation of the cystic duct there were extensive fibrosis and a nubbin gallbladder. While after splitting the gallbladder or taking a specimen for biopsy adhesions resulted, there was no extensive fibrosis or contraction of the wall. Permanent obstruction of the cystic duct was followed by hydrops only once and infection once, with a small abscess in the adjacent liver.

There was no bile sand in the common duct when the cystic duct was obstructed, although it was dilated in 88 per cent of the experiments. This is suggestive that the sand in the common duct may be formed in the gallbladder after traumatic or chemical changes.

Bile sand was found in five of seven experiments in which the gallbladder was split and a temporary ligature applied to the cystic duct; it was in the reconstructed gallbladder of four and in the common duct of two.

After the intravenous injection of dye without operation, bile sand or crystals were found in the gallbladder in three of twelve experiments.

After the injection of various solutions into the gallbladder without obstruction in thirteen experiments, a precipitate of bile was found once at the site of ligation. Mild chemical cholecystitis was usually present. Sepsis occurred only after obstruction of the common duct.

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[45] McWhorter, G. L.: New Methods of Anastomosis of the Common Bile Duct, Arch. Surg. **18**:117 (Jan.) 1929; Experimental Suture of the Common Bile Duct with New Methods of Anastomosis: Results After Two and One-Half Years, S. Clin. North America **12**:163 (Feb.) 1932.

In thirty-three experiments on dogs in which the cystic duct was patent at necropsy, bile sand was found in eight gallbladders, or 24 per cent. There was either trauma to the gallbladder by incision and puncture or some chemical disturbance after the intravenous injection of the dye. No changes occurred in rabbits.

In the absence of trauma, precipitation of bile may follow chemical changes or irritation of the biliary tract, with a disturbed secretion, absorption or impaired emptying mechanism.

DATA OF OTHER AUTHORS

Some of the changes observed in the gallbladder may be analogous to those found in the urinary bladder by Graves and Davidoff.[46] After the injection of hypertonic solutions of sodium bromide or chloride into the bladder, they found edema, thrombosis, multiple hemorrhages, surrounding fibrinous adhesions and paralysis of the muscle, but not after the injection of isotonic solutions or a 14.56 per cent solution of sodium iodide. Goldstein and Abeshouse[47] found a 12.5 per cent solution of sodium iodide irritating but less so than a solution of sodium bromide. Emmett[48] found sodium iodide irritating clinically in the presence of cystitis. Weld[49] found absorption of a 25 per cent solution of sodium bromide without irritation in the renal pelvis, but Braasch and Mann[50] found that with retention an abscess might result.

The frequency of edema in some of these experiments on the gallbladder with little microscopic evidence of cellular infiltration may be explained in the absence of infection by an effort of the blood to act as a fixing agent or diluent to the irritating agent (Aldrich[51]) with a collection of abnormally large amounts of fluid in the tissues. In the presence of edema, stasis of bile may easily result because of obstruction. The intravenous injection of diluted solution of sodium hypochlorite was followed by chemical inflammation of the gallbladder (Mann[52]), but formation of stones was not reported.

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[46] Graves, R. C., and Davidoff, L. M.: The Choice of Pyelographic Mediums, J. A. M. A. **80**:168 (Jan. 20) 1923.

[47] Goldstein, A. E., and Abeshouse, B. S.: Historical and Practical Consideration of Pyelographic Media, Am. J. Roentgenol. **33**:165 (Feb.) 1935.

[48] Emmett, J. L.: Elliott Treatment of Chronic Urethritis of Women: Preliminary Report, Proc. Staff Meet., Mayo Clin. **10**:545 (Aug. 28) 1935.

[49] Weld, E. H.: Renal Absorption with Particular Reference to Pyelographic Mediums, M. Clin. North America **3**:713 (Nov.) 1919; The Use of Sodium Bromid in Roentgenography, J. A. M. A. **71**:1111 (Oct. 5) 1918.

[50] Braasch, W. F., and Mann, F. C.: Effect of Retention in the Kidney of Media Employed in Pyelography, Am. J. M. Sc. **152**:336 (Sept.) 1916.

[51] Aldrich, C. A.: Clinical Course of Generalized Edema, with Suggestions as to Its Possible Function, J. A. M. A. **84**:481 (Feb. 14) 1925.

[52] Mann, F. C.: Production by Chemical Means of a Specific Cholecystitis, Ann. Surg. **73**:54 (Jan.) 1921.

Carter[53] found that in patients with typical symptoms of a disturbance of the gallbladder whose filling and emptying times were normal and whose roentgenograms showed no positive or negative shadows of stones, enlargement of the gallbladder, which is a result of stasis, was an important sign and was frequently present when stones were found at operation.

In four experiments I observed marked enlargement of the gallbladder after one week's starvation with water alone or with dextrose and water. The type of diet previous to visualization may affect the size of the gallbladder.

CLINICAL APPLICATION OF EXPERIMENTAL DATA

There appears to be a tendency to the formation of stones with stasis after partial or complete loss of function of the gallbladder and after trauma and certain chemical changes in the bile. However, no stones were found in the gallbladder in many experiments in which careful removal of a small section of the fundus was followed by suture and only once at the site of ligation of a needle puncture wound with silk. A thickened scarred wall did not seem to predispose to stones, although an unhealed area did.

The common duct will dilate and assume a part of the missing function of the gallbladder if the terminal sphincter is competent. The rôle of stasis is important in the formation of stones and infection and is dependent to a large extent on changes occurring at the outlet of the gallbladder and the common duct. It is easily seen how even small bile crystals or sand may produce varying degrees of spasm, inflammation or stricture when caught in the folds of mucosa or the glandular crypts, shown by Dardinski[54] to exist in the papilla of the common duct.

Infection was not found in experiments in which precipitated gallstones were found.

Biliary stasis may result clinically from physiologic disturbances after irregular or selective eating and particularly during an illness with gastro-intestinal disturbances.

Factors of surgical importance are the relief of inflammation, the removal of stones or particles, the correction of stasis and the restoration of maximum function.

Gallstones may result from systemic biliary changes, stasis or infection or in some instances from a combination of these factors. Clinically, stones may persist in the bile ducts for years with only vague disturbances until acute obstruction or infection occurs. In the majority of patients stasis or intermittent obstruction with gallstones usually results in fibrosis and chronic inflammation with some impairment of function and the absence of roentgenographic visualization of the gallbladder.

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[53] Carter, R. F.: Enlargement of the Gallbladder, Ann. Surg. **102:**194 (Aug.) 1935.

[54] Dardinski, V. J.: Anatomy of Major Duodenal Papilla of Man, with Special Reference to Its Musculature, J. Anat. **69:**469 (July) 1935.

When there is nonvisualization it is rather common to see the outline of a fibrotic gallbladder in the roentgenogram. This is probably due to repeated attacks of partial or intermittent obstruction. The changes in the biliary tract also vary with the extent of the infection which tends to persist with gallstones as with kidney stones. There may be no permanent loss of function after temporary obstruction in the ducts, and such gallbladders may be conserved.

From clinical and experimental observations of the frequent presence of precipitated particles of bile or sand, I am convinced that enough attention has not been given to their importance in the production of stasis. Both the cystic duct with its tortuous and valvular outlet, and the terminal portion of the choledochus, with its papilla lined with numerous gland crypts and rosebud folds of mucous membrane, are vulnerable points for obstruction by inflammation from minute particles of bile precipitate.

Obstruction or incarceration from a stone in either of these ducts and infection are frequently seen.

That minute particles of bile precipitate occur rather frequently and may be caught in the valves of the cystic duct or crypts of the papilla is not generally recognized.

Small foreign particles within the cystic or terminal portion of the common duct may lead to spasm, stasis, incarceration, traumatic inflammation and secondary local or extending infection. Primary infections in the bile ducts or extensive lymphangitis may occur without gallstones.

It is known that the liver (E. A. Graham and co-workers[55]) and also the lymph glands of the biliary tract (Judd) may contain pathogenic bacteria, although in the absence of stasis or acute inflammation it is rather unusual to find them in the bile.

An edematous inflamed gallbladder is not due to venous obstruction (Kreider[56]), and I have never found it after experimental ligation of both the cystic artery and the vein, but it resembles acute lymphangitis which extends into the liver.

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[55] Graham, E. A.: Hepatitis, Surg., Gynec. & Obst. **26**:521 (May) 1918. Graham, E. A.; Peterman, M. G., and Priest, W. S.: Association of Hepatitis with Experimental Cholecystitis and Its Bearing on Pathogenesis of Cholecystitis in the Human, Arch. Surg. **2**:92 (Jan.) 1921.

[56] Kreider, P. G.: Anatomy of Veins of Gallbladder: Their Relation to Impacted Stone, Surg., Gynec. & Obst. **57**:475 (Oct.) 1933.

I believe that the removal of the gallbladder, necessitating the opening of acutely inflamed lymph channels and glands, which Judd and others have found frequently to contain streptococci, or when the bile contains bacteria, may lead to a fatal lymphangitis, peritonitis or hepatitis and cholemia.

If one can diagnose mechanical obstruction of the cystic duct, early operation is decidedly preferable before the development of acute lymphangitis, empyema, cholangeitis or hepatitis with dehydration and toxemia.

If operation is not performed early, one should limit the procedure, if possible, to simple drainage of the gallbladder or ducts. In the presence of infection in the biliary tract or liver, two stage operations may be necessary to remove the gallbladder or stones from the common duct and occasionally from the cystic duct. Smears of the bile for bacteria should be made more freequently at operation. In the presence of bacteria, especially streptococci, one should usually limit the operation to drainage.

Under certain critical conditions the removal of only the mucosa may be indicated (W. J. Mayo[57]). Partial excision of the gallbladder (as practiced by Estes[58]) or partial excision and destruction of the unexcised mucosa of the wall of the gallbladder adherent to the liver with cautery (Rutherford Morison) or by electrocoagulation (Thorek[59]) should be of definite value in limiting infection. These procedures avoid opening the large anastomosing vascular, lymph and biliary channels and prevent the extension of the infection into the liver.

In the absence of biliary stasis or infection there are disadvantages in drainage of the gallbladder which seriously impairs function, although there is a low mortality, and in cholecystectomy, which produces changes in the common duct and liver.

CLINICAL STUDIES

A study of the physiology, operative results and experimental findings indicates that immediate suture of the gallbladder may be desirable under the following conditions: (1) after negative exploration of the gallbladder; (2) after removal of gallstones, especially a solitary one with good function of the gallbladder; (3) in a patient who is old or is a bad risk, after removal of stones in a functionless gallbladder but without inflammation or stasis in the biliary tract; (4) after cholecystotomy, when the common duct is opened and drained in the absence of acute inflammation, and (5) after excision of a solitary benign tumor in the wall of a functioning gallbladder.

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[57] Mayo, W. J.: Cholecystectomy, J. A. M. A. **35**:1396 (Dec. 1) 1900.

[58] Estes, W. L.: Partial Cholecystectomy, Arch. Surg. **23**:119 (July) 1931

[59] Thorek, M.: Electrosurgical Obliteration of the Gallbladder, J. A. M. A **103**:169 (July 21) 1934.

The following cases in which cholecystotomy with primary suture was done illustrate when this procedure may be indicated and demonstrate that function of the gallbladder may be preserved.

CASE 1.—*Solitary large gallstone impacted in the neck of the gallbladder with hydrops and chronic cholecystitis, angina pectoris and diabetes mellitus.*

B. A., a moderately obese man aged 49, had frequent attacks of angina and chronic myocardial damage. Subtotal thyroidectomy was performed two years previously for hyperthyroidism, although the patient was a bad surgical risk. Severe attacks referable to the gallbladder occurred over ten years, with almost constant pain and distress the last fifteen months, which was aggravated on eating. The patient had been under treatment for several years for marked diabetes. The blood pressure was 200 systolic and 120 diastolic. On March 29, 1933, and on April 14, 1934, roentgen examinations failed to visualize the gallbladder.

On May 2 operation revealed hydrops of the gallbladder with a wall 4 cm. thick due to complete obstruction of the neck by a solitary incarcerated cholesterol stone, measuring 2 by 2.5 cm. in diameter. The liver was moderately enlarged, and the surface was thickened. There was a palpable lymph gland along the cystic duct. An incision was made in the fundus, and the incarcerated gallstone was milked up and removed. The cystic duct was found to be patent, and the incision was closed with two rows of fine catgut. The wound was closed without drainage. On June 22, seven weeks after operation, roentgen examination failed to visualize the gallbladder. On Dec. 22, 1934, Feb. 8, 1935, and Feb. 18, 1936, there was good visualization of the gallbladder with emptying one hour after a fatty meal, and there was a normal duodenal bulb after a meal of barium sulfate. On February 23 there was complete relief from the symptoms referable to the gallbladder but a persistence of the attacks of angina. The patient was active but considerably overweight.

CASE 2.—*Solitary large stone with chronic cholecystitis and attacks of intermittent obstruction.*

J. D., a poorly nourished man aged 68, had attacks of gallbladder colic for the past eight years which became more frequent and finally occurred once or twice a week, with pain and tenderness over the upper portion of the abdomen. On June 24, 1935, roentgen examination failed to visualize the gallbladder. The Wassermann reaction was negative, and the icterus index, 5.

On July 8 operation revealed a moderately enlarged and thickened gallbladder with one gallstone, measuring 3.2 by 1.7 by 1.4 cm. in diameter. No stones or pathologic process was found in the ducts. The cystic duct was patent. There was moderate chronic hepatitis. An incision was made in the fundus of the gallbladder, the stone was removed and the edges of the wound were sutured with fine catgut sutures. The abdominal wound was closed without drainage. Mild pneumonia developed postoperatively in the lower lobe of the right lung, which was demonstrated roentgenographically. Microscopic examination of the gallbladder showed a normal wall, except for an increase in small round cells around the blood vessels of the subserous tissue. The patient was discharged from the hospital on August 1, with no complaints. On September 18 roentgen examination failed to visualize the gallbladder. On October 1 examination gave negative results, and the patient was relieved of his symptoms.

CASE 3.—*Solitary stone in the gallbladder. Acute attacks of auricular fibrillation and tachycardia with coronary and myocardial damage.*

M. S., a slightly obese woman aged 56, had severe attacks of auricular fibrillation and tachycardia with occasional collapse for a few months preceding operation. She suffered from abdominal distress with gas and belching at times but no colic. An electrocardiogram taken during an attack showed auricular fibrillation with tachycardia and mild myocardial and coronary damage. Complete roentgen studies of the gastro-intestinal tract, the kidneys and the chest gave negative results as did the laboratory examinations. The blood was normal. The roentgenogram showed good visualization and normal function of the gallbladder, which contained one large gallstone.

Operation on Oct. 7, 1935, showed a slightly enlarged gallbladder which contained one large cholesterol stone. There was slight chronic hepatitis. An incision was made in the fundus of the gallbladder, which appeared normal grossly, and the stone was removed. The incision was sutured carefully with fine catgut, and a piece of omentum was sutured over it. A small drain was left in the abdomen for twenty-four hours. Recovery was uneventful, and the patient was discharged from the hospital on the twelfth day. On Jan. 15, 1936, she had one mild cardiac attack. On February 18 roentgen examination showed good visualization and function of the gallbladder. On May 27 there were no further cardiac attacks or complaints.

CASE 4.—*Small adenoma of the fundus of the gallbladder. Chronic duodenal ulcer with high grade retention.*

W. C., a well developed man aged 49, who was moderately emaciated, presented a typical history of ulcer with periods of distress from two to three hours after meals for five years. There was a loss of 55 pounds (24.9 Kg.) of weight and constant distress after eating in the year preceding operation. Some relief was obtained by the ingestion of milk or mucin. Frequent attacks of vomiting occurred a few months before operation. During two weeks' treatment for ulcer in the hospital 1,000 cc. of the contents of the stomach was aspirated each night. There was no history of colic or pain referable to the gallbladder. The stools showed blood constantly.

Operation on July 14, 1934, revealed a characteristic chronic duodenal ulcer with a high grade stenosis and a few adhesions to the side of the gallbladder. A posterior gastrojejunostomy was performed. There was a small nodule in the fundus of the gallbladder 1 cm. in diameter. This nodule was excised, including the entire thickness of the wall of the gallbladder. The mucosa was inspected through the incision, but no other changes were seen. The incision was sutured with fine catgut and covered with omentum. The abdominal wound was closed without drainage. Convalescence was uneventful. The microscopic diagnosis was benign adenoma of the gallbladder. The patient was discharged from the hospital on Aug. 1, 1934. On August 25 a roentgenogram showed some visualization of the gallbladder. On September 17 the patient had no complaints. There was a gain of 30 pounds (13.6 Kg.) in weight after the operation.

Comment.—Cholecystotomy with primary suture of the gallbladder was performed on three of the four patients for removal of solitary stones and on the fourth for an adenoma of the fundus, which was excised. All of the patients were poor risks; two had symptoms of severe cardiac damage, the third was 68 years old and poorly nourished and the fourth was emaciated and had a high grade stenosis due to a duodenal ulcer. In all but the third case, in which a drain was removed on the second day, the abdominal wounds were closed without drainage. None of the patients have had any evidence of recurrence of gallstones. In three of the four cases the function of the gallbladder was demonstrated after operation by roentgenographic visualization.

In the first case, in which the gallbladder was thickened and the cystic duct obstructed, there was no visualization seven weeks after operation, but at six months and one and one-half years there was good function. In the second case, in which a thickened chronically inflamed gallbladder was found at operation, there was no visualization after five weeks, and no further tests have been made. In the third case, in which function was normal before operation, there was good visualization when the patient was tested after four months. In the fourth case there was some visualization after five weeks.

It is shown here that with a normal or even a considerably thickened gallbladder due to intermittent or complete obstruction function may return in from five to ten weeks after cholecystotomy with primary suture.

DISORDERS OF THE COMMON DUCT

Recent statistics point to an increasing frequency of stones developing in the common duct after removal of the gallbladder or after loss of function (Judd,[60] Beye[61] and Hunt[62]).

Evidence is given by Rufanov[63] of the occasional development of stones in the substance of the liver or the intrahepatic bile ducts (Rovsing[64]). This indicates that measures other than removal of the gallbladder, such as the correction of diet, removal of foci of infection and proper exercises, are necessary in the presence of a diathesis to gallstone formation.

The common duct as a rule is found dilated after removal of the gallbladder (Judd and Mann), although there may be a temporarily incompetent sphincter.

If the sphincter remains incompetent, Rost[65] has observed that there is no compensatory dilatation of the common duct.

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[60] Judd, E. S.: Disease of the Biliary Tract, S. Clin. North America **15**:1073 (Oct.) 1935.

[61] Beye, H. L.: Conditions Necessitating Surgery Following Cholecystectomy, Tr. West. S. A. **44**:450, 1934.

[62] Hunt, V. C.: Liver in Relation to Surgical Treatment of Lesions of Extrahepatic Bile Ducts, California & West. Med. **43**:278 (Oct.) 1935.

[63] Rufanov, Ivan G.: Liver Stones, Ann. Surg. **103**:321 (March) 1936.

[64] Rovsing, T.: Gallstones Cause, Not the Result of Infection, Acta chir. Scandinav. **56**:207, 1923.

[65] Rost, F.: Die funktionelle Bedeutung der Gallenblase, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:710, 1913.

The tone of the sphincter may be partially or completely gone, thereby lessening biliary stasis and the tendency to the formation of stones without necessarily causing the loss of the protecting folds of mucosa in the papilla with regurgitation from the duodenum.

A spastic or stenosed sphincter may predispose to infection or to the formation of stones, especially in the presence of a diathesis. The occurrence of gallstones in the gallbladder is much less serious than in the common duct.

A fibrotic gallbladder may be left under certain conditions, especially if the cystic duct is found to be dilated, and the operation may be limited to the relief of stasis of the common duct.

One should attempt to produce a moderate amount of incompetency of the sphincter of the common duct when biliary stasis is due to spasm, papillitis, ampullitis or cholangeitis, either with or without gallstones.

If stasis is due to acute inflammation of the biliary tract or pancreas, simple biliary drainage will usually permit the swelling to subside.

When considerable resistance is found at the outlet of the common duct, cautious dilatation may be followed in certain instances by the use of an indwelling catheter.

Diminution of the action of the sphincter may be obtained by cutting, by dilatation or by leaving a rubber tube in it.

Cutting the sphincter should be done through a duodenotomy incision and followed by a plastic suture. Unless deep cuts are made in the wall of the duodenum, there will be no permanent dilatation. If severe dilatation or deep cuts are attempted through the common duct, the wall may be perforated, with leakage and peritonitis (Allen [66] and Lahey [67]). Experimentally, I [68] observed that dilatation of the sphincter by a pressure of 250 mm. of mercury produced only a temporary decrease in tone. Severe instrumental dilatation was necessary to produce permanent dilatation, as measured several weeks later. Moderate dilatation resulted in a decrease of the resistance of the sphincter to about one-half normal.

A rubber tube passed through the sphincter and left for some time produced some permanent dilatation, but cultures taken later from the liver were frequently positive, suggesting ascending infection. Normally the sphincter and papilla guard the bile ducts from ascending parasites, foreign bodies and infection. Under certain pathologic or anatomic conditions of the bile passages and possibly also of the pancreas, a diminution of its action may be desirable. In the presence of a high grade congenital or fibrous stenosis anastomosis of the biliary tract to the stomach or duodenum may be necessary. Recent experimental work of Gentile[69] indicates that the danger of ascending infection in the absence of stasis has been overemphasized.

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[66] Allen, A. W.: Diagnosis and Treatment of Stones in the Common Bile Duct, Surg., Gynec. & Obst. **62:**347 (Feb.) 1936.

[67] Lahey, F. H.: Stones in the Gallbladder and Bile Ducts, S. Clin. North America **15:**1459 (Dec.) 1935.

[68] McWhorter, G. L.: The Surgical Significance of the Common Bile Duct Sphincter, Surg., Gynec. & Obst. **32:**124 (Feb.) 1921.

In deciding whether operation is indicated in disease of the biliary tract one must be guided by the gross appearance of the liver, the common duct and the gallbladder.

A small common duct with a thin wall should indicate that the disease was limited to the gallbladder or that there was a primary incompetent sphincter. A dilated common duct with a slightly hypertrophied wall might indicate a competent sphincter with a functionless gallbladder or the absence of the gallbladder. Exploration of the duct would not necessarily be indicated in either condition.

A dilated common duct with a thin wall associated with jaundice but without stones in the gallbladder would suggest high grade or complete obstruction at the outlet of the duct by carcinoma, local inflammation or extramural pressure.

A common duct with a thick muscular wall and some dilatation would suggest incomplete or intermittent obstruction.

A dilated fibrotic common duct associated with jaundice and stones in the gallbladder would suggest an obstruction at the terminal portion of the duct by stones or by a stenosis with infection. Exploration of the common duct and occasionally anastomosis of the gallbladder would be indicated.

Bernhard[70] reported on a thousand choledochotomies, with a mortality of 9.9 per cent, there being three times more men than women in his group of patients. Icterus was the chief indication, this symptom being absent in only 19 per cent. Among the patients followed up after operation, about one-third had some complaints and 11 per cent had severe complaints, usually due to cholangeitis and hepatic damage, while recurrence of stones was rare. Chronic pancreatitis was present at operation in about 10 per cent.

OPERATIONS ON THE COMMON DUCT AND GALLBLADDER

The following cases illustrate six different pathologic conditions of the common duct in which primary suture of the duct, gallbladder or of both was done.

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[69] Gentile, A.: Cholecystogastrostomy and Hepatitis: Experimental Study, Arch. Surg. **30**:449 (March) 1935.

[70] Bernhard, F.: Ueber die Erfahrungen bei 1000 Choledochotomien aus den Jahren 1895-1932 und ihre Spätergebnisse auf Grund von Nachforschungen bzw. Nachuntersuchungen, Deutsche Ztschr. f. Chir. **246**:1 (Dec. 10) 1935.

Case 1.—*Gallstones in the gallbladder and common duct. Patent ampulla, but recent obstructive jaundice. Cholecystolithotomy and choledocholithotomy* (fig. 1*A*).

A. S., a man aged 62, after six weeks of complete jaundice underwent an exploratory operation five months before the present operation, and a clinical diag-

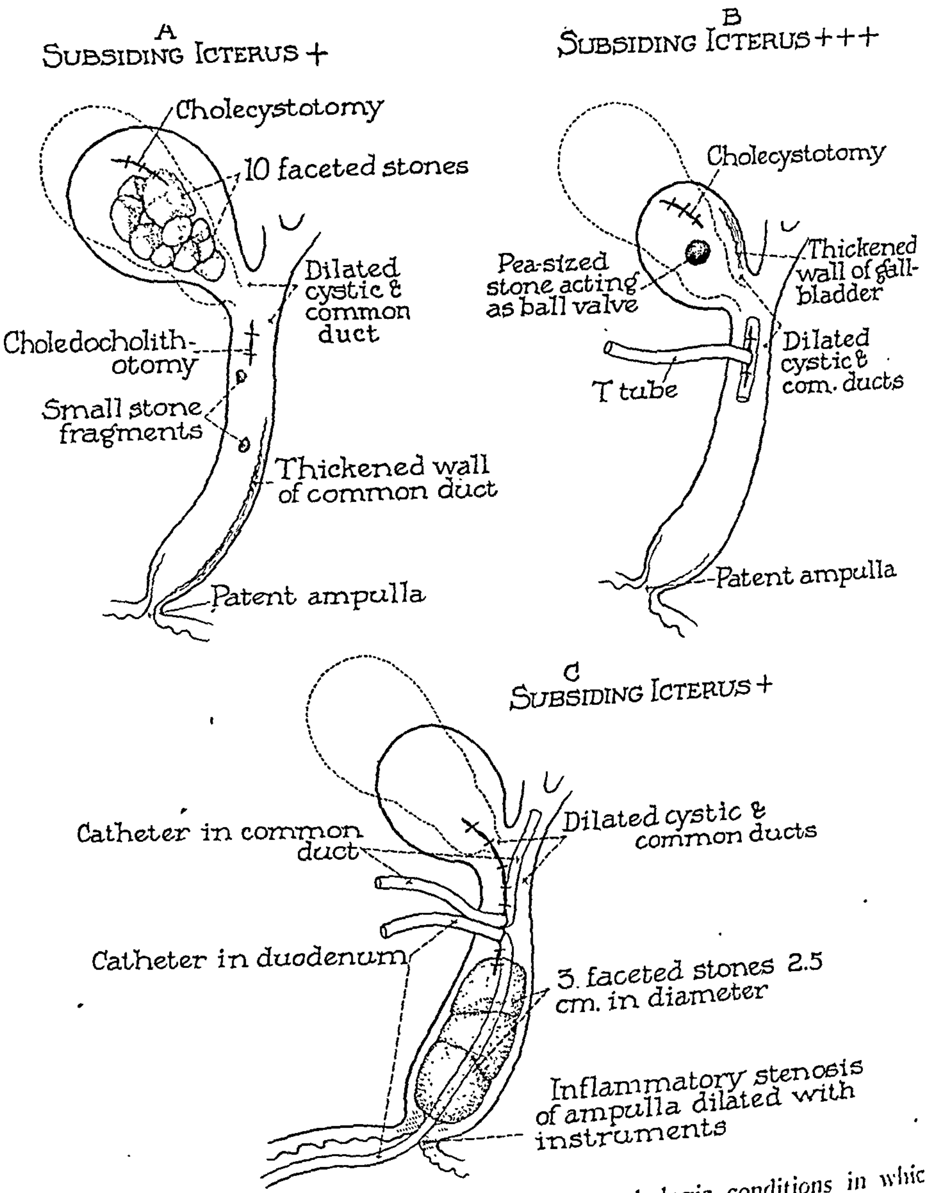
A
Subsiding Icterus +
Cholecystotomy
10 faceted stones
Dilated cystic & common duct
Choledocholithotomy
Small stone fragments
Thickened wall of common duct
Patent ampulla
B
Subsiding Icterus +++
Cholecystotomy
Pea-sized stone acting as ball valve
Thickened wall of gall-bladder
Dilated cystic & com. ducts
T tube
Patent ampulla
C
Subsiding Icterus +
Catheter in common duct
Dilated cystic & common ducts
Catheter in duodenum
3 faceted stones 2.5 cm. in diameter
Inflammatory stenosis of ampulla dilated with instruments

Fig. 1—Diagrammatic drawing showing three pathologic conditions in which different operations were performed on the common duct and the gallbladder with primary suture of duct in one (*A*) and of the gallbladder in all (*A*, *B* and *C*).

nosis of inoperable carcinoma of the pancreas was made; the gallbladder was drained. The present complaints were complete obstructive jaundice of five weeks' duration with acholic stools. Recently the jaundice subsided suddenly to only a trace. On Aug. 16, 1934, roentgen examination failed to visualize the gallbladder, but the thick walls cast a shadow.

When operation was performed on August 30 there was slight icterus. Ten large faceted stones were removed from the moderately thickened gallbladder, followed by primary suture. Two small crumbs of a stone were removed from a slightly thickened common duct, which was closed by primary suture after the ampulla was found to be patent to a no. 12 French catheter. An incisional hernia was repaired, and an abdominal drain was inserted through a stab incision. Recovery was uneventful. The patient was discharged from the hospital on September 17.

CASE 2.—*Small solitary gallstone in the gallbladder with dilated cystic and common ducts. Patent ampulla but a recent obstructive jaundice and extensive fibrosis of the biliary tracts. Cholecystolithotomy and choledochostomy* (fig. 1*B*).

T. C., a man aged 46, suffered from an extensive myocardial damage with fibrillation and hemiplegia for one year. He had marked obstructive painless jaundice of two months, which was slightly decreasing. On Aug. 21, 1935, the icterus index was 80. The stool contained blood but no bile. On August 24 the icterus index was 54.

At operation on September 6 a "ball valve" stone, 0.7 cm. in diameter, was removed from a small fibrosed gallbladder with a dilated cystic duct 1 cm. in diameter. Primary suture of the gallbladder was done. In order to prevent any later bleeding, a fine catgut suture was tied about the cystic duct and blood vessels. The mucosa of the terminal end of the common duct was thickened and friable, and the ampulla was patent and contained no stones. A T tube was inserted. The jaundice cleared up in three weeks. Four weeks after the operation the T tube was removed. Recovery was uneventful. The patient was discharged on September 30.

CASE 3.—*Large gallstones in the common duct with a slight inflammatory stenosis of the ampulla. Extensive fibrosis of the biliary tract, with dilated cystic and common ducts and a small gallbladder. Cholecystotomy and choledocholithostomy* (fig. 1*C*).

L. K., a man aged 64, had had acute symptoms characteristic of attacks of gallbladder disease for several years, with recent attacks of jaundice, vomiting, clay colored stools and soreness in the right upper quadrant but no pain. There was a recent jaundice of three weeks' duration. On Oct. 30, 1935, the icterus index was 30, and the cholesterol content, 150. On November 7 the gallbladder was faintly visualized. Roentgenograms of the gastro-intestinal tract were normal.

When operation was performed on November 8 there was slight icterus and the gallbladder was found to be small and fibrosed. Three 2 cm. faceted and partially embedded stones were removed from a dilated common duct, and the incision was continued into the dilated cystic duct and gallbladder, which had no stones. The inflammatory stenosis of the ampulla was dilated, and a no. 12 catheter was inserted into the duodenum and brought out through the wound. A second catheter was placed in the hepatic duct. The incision into the gallbladder and cystic duct was sutured tightly. A scar of a duodenal ulcer was present. After a few days the bile formed a precipitate in the drainage tube, making daily irrigation necessary. The tubes were removed after three weeks. Recovery was uneventful. On December 8 the icterus index was 6. The patient was discharged on December 8. At examination on Jan. 10, 1936, no complaints were elicited.

CASE 4.—*Complete stricture of the common duct and obstruction of the cystic duct by a stone with empyema and multiple stones in the gallbladder. Choledochotomy with flap duodenocholedochostomy and cholecystolithectomy* (fig. 2*D*).

P. L., a woman aged 70, had had many previous mild attacks referable to the gallbladder. The blood pressure was 210 systolic and 90 diastolic. There was complete obstructive jaundice of three weeks' duration with chills and fever but no colic. On Sept. 13, 1935, the icterus index was 88, and on September 17, it was 92. There was blood but no bile in the stools. Roentgen examination, which was done elsewhere, failed to visualize the gallbladder. The condition of the patient became progressively worse.

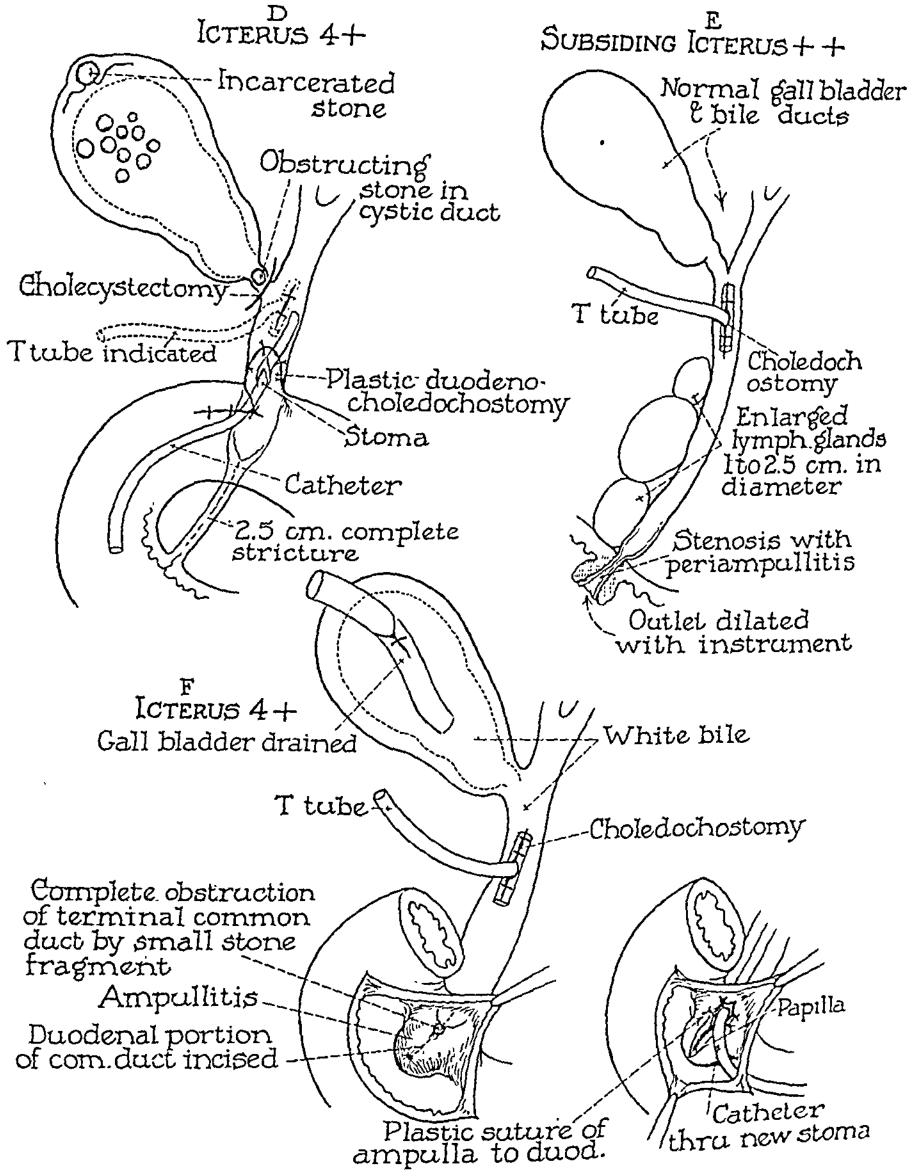
D
Icterus 4+
Incarcerated stone
Obstructing stone in cystic duct
Cholecystectomy
T tube indicated
Plastic duodeno-choledochostomy
Stoma
Catheter
2.5 cm. complete stricture
E
Subsiding Icterus++
Normal gall bladder & bile ducts
T tube
Choledochostomy
Enlarged lymph.glands 1to2.5 cm. in diameter
Stenosis with periampullitis
Outlet dilated with instrument
F
Icterus 4+
Gall bladder drained
White bile
T tube
Choledochostomy
Complete obstruction of terminal common duct by small stone fragment
Ampullitis
Duodenal portion of com.duct incised
Plastic suture of ampulla to duod.
Papilla
Catheter thru new stoma

Fig. 2.—Diagrammatic drawing showing operations on the common duct, with dilation of the outlet and without disturbing the gallbladder (*E*) and with plastic correction of a terminal stenosis (*D* and *F*) and combined with removal of the gallbladder (*D*) or with drainage (*F*).

Operation on October 1 showed the liver to be green and the gallbladder enlarged and indurated with mucopurulent contents and stones. One was embedded in the necrotic mucosa of the fundus and one completely obstructed the small cystic duct. The gallbladder and stones were removed. The common duct was enlarged except the terminal 3 cm., which was indurated, forming an impassable stricture. Choledochoduodenostomy was performed, with a duodenal flap sutured around an opening low in the common duct over a rubber tube. The opening in the common duct was sutured tightly, with drainage of the abdominal wound. The temperature was 103 F. for the first two days postoperatively. The patient improved until the ninth day, although there was a biliary fistula, when cardiac decompensation and death suddenly occurred.

CASE 5.—*Stenosis of the ampulla due to pericholedochitis at the terminal portion and pressure from enlarged lymph glands. Normal gallbladder and common duct with absence of stones. Obstructive subsiding jaundice. Subacute chronic appendicitis. Choledochostomy with T tube; dilatation of sphincter; appendectomy (gallbladder undisturbed)* (fig. 2*E*).

S. F., a Negro aged 35, gave a history of repeated alcoholic bouts. He had had obstructive painless jaundice for five weeks, which was gradually subsiding. On Oct. 2, 1935, the gallbladder was palpable. The icterus index was 105. Drainage with a duodenal tube gave no relief. Roentgen examination of the gastrointestinal tract gave negative results. The jaundice became less marked.

At operation on October 28 the gallbladder and walls of the common duct appeared to be normal. The common duct was opened, but no stones were found. There was slight stenosis of the ampulla, which was dilated, and a T tube drain was inserted. Five large lymph glands were removed from the side of the common duct. A kinked subacutely inflamed appendix was removed. The microscopic report on the glands along the common duct, measuring from 1 to 2 cm., was simple hyperplasia. After the injection of iodized poppy-seed oil 40 per cent through the T tube on November 16 visualization showed the outlet to be patent, and the tube was removed. The icterus index on November 8 was 31, and on November 15 it was 8. Convalescence was uneventful. The patient was discharged on November 27. Observation on Jan. 10, 1936, elicited no complaints. On April 8 slight visualization of the gallbladder was observed. On May 25 the patient was in excellent condition with no complaints, although he frequently became inebriated.

CASE 6.—*Complete inflammatory stricture of the ampulla of the common duct around a gallstone crumb, with "white" bile and subacute cholecystitis. Cholecystostomy, choledochostomy and duodenotomy with ampulloduodenorrhaphy and ampullolithostomy* (fig. 2*F*).

F. C., a woman aged 24, had had painful attacks referable to the gallbladder for one year. The present attack associated with vomiting and jaundice began five weeks before operation, becoming complete ten days before. The icterus index on Aug. 22, 1935, was 63; on August 24 it was 74, and on August 28 it was 96.8. The hemoglobin content was 58 per cent; the red blood cells numbered 4,560,000, and the white blood cells, 11,950. The stools were acholic. A transfusion of blood was given.

At operation on September 9 the liver was found to be congested, and the gallbladder and common duct were enlarged and thickened. They were opened and found to contain white bile, but no stones were seen. There was complete obstruction at the ampulla due to a palpable spherical mass. The duodenum was opened, and the papilla and ampulla were found to be surrounded by an inflammatory mass 2 cm. in diameter. The papilla was split open, and an inflammatory stenosis with a small crumb of a gallstone was found incarcerated in the end of the ampulla. The cut sides of the ampulla were sutured to the duodenum, a short rubber tube was inserted into the common duct and the duodenum was closed. A tube was also inserted in the common duct and a drainage tube in the gallbladder. The gallbladder drain was removed after three weeks and the T tube after four weeks. There was uneventful convalescence. The patient was discharged on October 9.

Comment.—These six cases with evidence of obstructive jaundice illustrate different problems in operations on the common duct in which an exploratory incision of all or a part of the biliary tract may be followed by primary suture alone or combined with drainage.

All six of the patients, with perhaps one exception (S. F.), were poor risks and suffered from jaundice, which was complete in two cases, with "white" bile in one. Three were over 60 years old, and one had severe cardiac damage. A careful study had been made of each patient before operation, and it was believed that nothing could be gained by further medical treatment.

In the first case, after jaundice for several weeks the gallbladder was drained owing to an incorrect diagnosis of inoperable carcinoma of the head of the pancreas, five months previous to a second operation. The ten faceted stones found at the second operation had undoubtedly formed since the first one, the formation being favored by biliary stasis. Primary suture of both the common duct and the gallbladder with the insertion of a safety drain in the wound was done to conserve function and to shorten the postoperative disability, since the ampulla was patent.

The patient in the second case was a bad risk because of the cardiac condition. There was a recent subsidence of an obstructive icterus. The common duct was patent, the cystic duct was dilated and the gallbladder was fibrosed and contained a small stone covered with fragments of mucous membrane, indicating recent impaction in the common duct. The incision in the gallbladder was sutured, and the common duct was drained with a T tube to relieve the icterus. Temporary occlusion of the cystic duct was done with a catgut ligature to prevent any later bleeding from the sutured incision.

In the third case the gallbladder was small and fibrotic and the common duct thickened and dilated with three large faceted stones in it, producing some necrosis of the mucosa and inflammatory stenosis of the outlet. This was dilated, and a small catheter was passed into the duodenum and another into the hepatic duct.

In the fourth case, in which the symptoms were complete obstructive jaundice, chills and fever, the patient was a poorly nourished woman of 70 years, with hypertension and cardiac damage. There was a complete stricture of the common duct. Anastomosis of the gallbladder to the stomach could not be done because there was an incarcerated stone in the cystic duct and an empyema of the gallbladder. The gallbladder and stones were removed. A flap was cut, and an anastomosis was made from the duodenum to the common duct. A catheter should have been left in the duct on account of the icterus and to relieve the pressure from the anastomosis. However, a leakage of bile developed along the abdominal drain, with no local reaction. The patient died of cardiac weakness on the ninth day, after an early hyperpyrexia had subsided. Simple drainage of both the common duct and the gallbladder might have given temporary relief, and a second operation could have been performed under better conditions. I[71] have previously reported the case of a patient in whom hepaticoduodenostomy was successful for over thirteen years.

In the fifth case a complete obstructive jaundice was subsiding. There was a normal appearing gallbladder and common duct, with compression by large lymph glands. The glands were removed, and exploration of the common duct showed it to be slightly narrowed at the outlet. It was dilated easily, and a T tube was inserted. The gallbladder, which appeared normal, was not opened. A subacutely inflamed appendix was removed. Either the large hyperplastic lymph glands or a primary papillitis may have obstructed the duct. There was a patent outlet, as shown after choledochography through the T tube, and complete recovery resulted. It is possible that an incompetent sphincter may have been the cause of the nonvisualization of the gallbladder seven months after operation, although the patient was free from symptoms.

In the sixth case there was a persisting complete obstructive jaundice. A thickened dilated gallbladder and common duct were explored, and both contained "white" bile without visible stones. An inflammatory mass in the region of the ampulla was found on incision after duodenotomy to be an inflammatory stenosis of the papilla surrounded by a zone of inflammation. When the papilla was incised a fine crumb of a gallstone not over 1 by 2 mm. in size was found incarcerated in the swollen mucosa. It was removed, and the cut sides of the ampulla were sutured to those of the duodenal mucosa around a small rubber tube. A T tube was placed in the common duct and a drain in the gallbladder. Convalescence was uneventful.

Gas with local anesthesia or local anesthesia alone was used in all of the clinical cases reported.

In the postoperative treatment of most patients after biliary operations one must guard against dilatation of the stomach, but continuous aspiration of the gastric contents with a catheter predisposes to bronchitis and pneumonia.

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[71] McWhorter, G. L.: Congenital Cystic Dilatation of the Common Bile Duct, Arch. Surg. 8:604 (March) 1924; Results of Reconstruction of Common Bile Duct, S. Clin. North America **12**:159 (Feb.) 1932.

The differential diagnosis of inflammatory stenosis of the ampulla, with or without stones, from a malignant growth of the ampulla, common duct or pancreas and chronic pancreatitis is difficult, particularly when there is blood in the stools and no pain. Inflammatory changes in the terminal portion of the common duct, with or without stones, should be considered more frequently as the cause of obstructive jaundice.

CONCLUSIONS

1. The frequency of gallstone particles or crumbs has been observed experimentally and clinically. It is probable that their clinical occurrence has been overlooked in causing transient colic or spasm and, when incarcerated in the ampulla or papilla, in the production of edema, stasis and infection of the ducts, liver, gallbladder and pancreas.

2. The biliary tract and liver easily react to chemical changes and trauma by inflammation, after which there may be precipitation of bile. Caution should be observed in the use of the dye or opaque mediums injected intravenously in the presence of inflammation or obstruction in the biliary tract.

3. Temporary ligation of the bile ducts with fine catgut may aid in controlling hemorrhage, especially about the cystic duct, and in the diversion of bile.

4. Experimentally, after splitting the gallbladder and occluding the cystic duct, healing occurs rapidly, usually with a tendency to fibrosis. In the absence of stones or infection there is no unusual change in the liver. Clinically, on the other hand, with obstruction and stones of the cystic duct, extensive inflammation of the gallbladder and liver, which may be due to infection, frequently occurs.

5. Conservation of the gallbladder in the presence of any function may prevent later changes in the common duct leading to stasis and the formation of stone. When indicated, exploratory opening and even wide splitting of the gallbladder may be done and may be followed by primary suture. The gallbladder may be left unopened when the disturbance is found to be limited to the common duct.

6. Primary suture of the gallbladder may more nearly restore physiologic function and avoid complications than either drainage or removal in selected cases. Drainage of either the gallbladder or the common duct is desirable in acute inflammation and stasis, but with extensive chronic disease cholecystectomy is usually indicated.

7. Leaving alone a functionless gallbladder, especially one with a dilated cystic duct, may be preferable, especially in a patient who is a poor risk, and probably will not increase the formation of stones in the common duct. Conservation of the gallbladder, when feasible,

will definitely lower the immediate mortality and make an operation for stones in the common duct or for stenosis safer. In the presence of biliary stasis or diathesis, gallstones may reform in either a functioning or a nonfunctioning gallbladder or in the common duct.

8. There is an increasing frequency of pathologic conditions of the common duct. This is due not only to the clinical frequency of systemic changes leading to disease of the biliary tract and primary disturbances in the terminal portion of the choledochus but to further changes in the common duct resulting from unnecessary drainage or removal of still functioning gallbladders.

9. Papillitis or ampullitis may exist with local inflammation and lymphadenopathy but with an otherwise normal biliary tract. This may arise from spasm and irritation of minute crumbs of gallstones and from extension of infection from the duodenum or other foci, such as appendicitis.

10. A better understanding of disturbances of the biliary tract and their pathologic changes should lead to earlier operation with more frequent correction of disorders of the common duct and to greater conservation of the gallbladder with better end-results and a lower mortality.

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THROMBO-ANGIITIS OBLITERANS AND TYPHUS

EVIDENCE OF ETIOLOGIC RELATIONSHIP

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The history of medicine makes it axiomatic that diseases of unknown etiology have given rise to innumerable measures for their relief. Success in therapy, however, with few exceptions, was attained only on the discovery of the causative factor. In this respect thrombo-angiitis obliterans is typical. The literature of the last three decades reveals hundreds of therapeutic suggestions which have been tried and which have yielded little success. This may be attributed to the fact that of all the peculiar etiologic agents which have been suggested, none up to the present time has proved to be the real cause of the condition. Among the causes which have been advanced may be mentioned ethnologic predisposition, metabolic disturbances, climatic and balneologic conditions, endocrine disturbances and syphilis. The toxic effects of drugs and chemicals, such as tobacco, alcohol and ergot, have also been suggested as the possible cause of the disease. However, none of these has as yet been proved.

ETIOLOGY

Race.—It has been generally believed that thrombo-angiitis obliterans is peculiar to the Jewish race, largely because a number of years ago the majority of cases observed in this country occurred among poor Jewish immigrants from Russia and Poland. As a matter of fact, this people has been so scattered and intermarried that a pure Jewish strain can scarcely be said to exist. In discussing this subject, Friedman[1] in 1920 stated that he had seen the disease in Estonians and Russians as well as in Jews. It has been noted chiefly among Jews because few Estonians and Russians have migrated to this country. At this time Frauenthal[2] said that he had seen over 900 cases of

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[1] Friedman, G. A., in discussion on Buerger, Leo: The Pathology of Thrombo-Angiitis Obliterans, M. Rec. **97**:457-458 (March 13) 1920.

[2] Frauenthal, in discussion on Buerger, Leo: The Pathology of Thrombo-Angiitis Obliterans, M. Rec. **97**:457-458 (March 13) 1920.

thrombo-angiitis obliterans and that 90 per cent of them were in Russian, Polish and Austrian Galicians; he believed, therefore, that the presence of the disease depended on location. Kukin[3] reported 70 cases in Russians, only 3 of whom were Jews. Schum[4] stated that in Russia the disease was just as common among gentiles as among Jews. Meleney and Miller[5] reported a series of 25 cases of thrombo-angiitis obliterans which occurred in China. Ludlow[6] saw over 100 cases in Korea, and Koga[7] spoke of the disease being common in Japan in 1913. Telford and Stopford[8] in 1924 reported 4 cases in non-Jewish British subjects. Weber, Rast and Lutterotti[9] also described 3 cases in Englishmen without Jewish ancestry and stated that they had seen other cases in the London hospital in persons apparently without Jewish ancestry. Huguenin, Albot and Moldovan[10] cited 3 cases in Frenchmen who were non-Jews, and Orr[11] reported 6 cases in American-born persons without Jewish ancestry. In discussing the etiology of thrombo-angiitis obliterans, Scupham[12] wrote that race should no longer be considered an important factor and reported in detail a case of the typical disease in a Negro. Ochsner stated that he encountered thrombo-angiitis obliterans among Scandinavians in Chicago, while Matas and others reported having seen it in native Americans in New Orleans and elsewhere.

Tobacco.—The prevailing opinion that tobacco enters largely into the causation of the disease does not appear to have a rational basis. Although many persons with thrombo-angiitis obliterans give a history of excessive smoking, in view of the greater use of tobacco an increasing incidence of the disease should be expected. Furthermore, since cigaret smoking has become a common custom, it would seem reasonable to expect to find more women afflicted with the disease. It is also worthy of note that in Russia and southeastern Europe, where thrombo-angiitis obliterans is of frequent occurrence, tobacco is a luxury beyond the means of the poor peasants. Harkavy[13] used tobacco pollen, tobacco and other allergens to test for hypersensitivity of the skin in over 200 smokers. The results did not indicate that smokers were more often sensitive to tobacco than to other allergens. Trasoff, Blumstein and Marks,[14] of Mount Sinai Hospital, Philadelphia, made similar tests with tobacco. They stated that their studies did not justify the contention that hypersensitiveness of the vascular system to tobacco is the mechanism of thrombo-angiitis obliterans and coronary disease. They stated that there was no essential difference in the reactivity of the skin of normal smokers and of nonsmokers to tobacco. Friedlander, Silbert and Laskey[15] administered daily intraperitoneal injections of extract of tobacco in Ringer's solution to rats. Of 48 male rats receiving these injections, gangrene of the toes developed in 33 in from five to twelve weeks. In none of 12 female rats treated for from five to six weeks did this lesion develop. In 10 control male rats living under identical conditions, no gangrene developed. The histologic changes in the vessels were not mentioned.

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[3] Kukin, N. M.: Obliterating Endarteritis in Women, Sovet. khir. (no. 1) **6**:40-43, 1934.

[4] Schum, H.: Das Krankheitsbild der juvenilen Gangrän, Beitr. z. klin. Chir. **146**:551-591, 1929.

[5] Meleney, F. L., and Miller, G. G.: A Contribution to the Study of Thrombo-Angiitis Obliterans, Ann. Surg. **81**:976-993 (May) 1925.

[6] Ludlow, A. I.: Thrombo-Angiitis Obliterans: A Review and Report of the Disease in Koreans, China M. J. **45**:487-514 (June) 1931.

[7] Koga, G.: Zur Therapie der Spontangangrän an den Extremitäten, Deutsche Ztschr. f. Chir. **121**:371-382, 1913.

[8] Telford, E. D., and Stopford, J. S. B.: Thrombo-Angiitis Obliterans, Brit. M. J. **2**:1035-1037 (Dec. 6) 1924.

[9] Weber, F. P.; Rast, H., and Lutterotti, O.: Thrombo-Angiitis Obliterans in Non-Hebrew Subjects, Brit. M. J. **2**:279-280 (Aug. 23) 1930.

[10] Huguenin, R.; Albot, R., and Moldovan, S.: A propos de deux cas de thrombo-angéite oblitérante chez des sujets non-israélites, Ann. d'anat. path. **8**: 176-183 (Feb.) 1931.

[11] Orr, T. G.: Thrombo-Angiitis Obliterans a Universal Disease, J. Missouri M. A. **22**:174-175 (May) 1925.

[12] Scupham, G. W.: The Diagnosis of Peripheral Vascular Diseases, Illinois M. J. **70**:516-521 (Dec.) 1936.

Alcohol.—As for alcohol, it has been found that in persons with arterial disease thought to result from chronic alcoholism the condition is not thrombo-angiitis obliterans.

Ergot.—There are on record[16] a few instances of a person's suffering from ergot poisoning due to overconsumption of diseased rye, but there has been no report of a case of thrombo-angiitis obliterans in such a person. Surely this cause could not be operative in China, where the staple diet is millet and rice, or in Japan, where the population subsists on fish and rice; moreover, a study of the histories of patients with thrombo-angiitis obliterans affords no evidence that ergot might be a causative factor. McGrath[17] and others have attempted to produce the disease by injection of ergotamine tartrate, but they do not claim that the lesions which developed were definitely those of thrombo-angiitis.

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[13] Harkavy, J.: Skin Sensitiveness to Extracts of Tobacco Leaf, Tobacco Pollen, Tobacco Seed and to Other Allergens in Two Hundred Normal Smokers, J. Allergy **6**:56-61 (Nov.) 1934.

[14] Trasoff, A.; Blumstein, G., and Marks, M.: Immunologic Aspect of Tobacco in Thrombangiitis Obliterans and Coronary Artery Heart Disease, J. Allergy **7**:250-253 (March) 1936.

[15] Friedlander, M.; Silbert, S., and Laskey, N.: Toe Lesions Following Tobacco Injections in Rats, Proc. Soc. Exper. Biol. & Med. **34**:156-157 (March) 1936.

[16] Kaunitz, J.: Chronic Endemic Ergotism, Arch. Surg. **25**:1135-1151 (Dec.) 1932.

Syphilis.—The view that syphilis might be an etiologic factor can be excluded, as Buerger and Kaliski found the Wassermann reactions of patients with thrombo-angiitis to be almost uniformly negative.

Metabolic Diseases.—Metabolic tests on persons with thrombo-angiitis obliterans made under my supervision at the Beth Israel Hospital gave results in no wise different from those obtained with the tests on normal subjects used as controls.

Climatic Conditions.—The fact that thrombo-angiitis obliterans occurs in almost all climates and latitudes makes a discussion of this question superfluous.

Infectious Origin.—The infectious origin of thrombo-angiitis obliterans was first suggested by Saltikow and later by Buerger,[18] who based his conviction on the following evidence: 1. An acute inflammatory lesion and occlusive thrombosis of the arteries and veins are characteristic lesions. 2. Mechanically and symptomatologically, the thrombotic occlusion is the most important phenomenon. 3. The thrombosis is probably preceded and certainly accompanied by an acute inflammatory stage. 4. The lesion involves deep veins in about 40 per cent and superficial veins of the upper and lower extremities in 20 per cent of the cases. 5. Recent investigations of the veins show that acute lesions in the superficial and in the deep vessels are identical. 6. Histologic changes in the veins point to the existence of an infective process.

Meleney and Miller, who observed 25 cases in Chinese subjects, stated that the source of the disease was of infectious origin. They added that careful search on the part of a number of investigators had failed to reveal any specific micro-organism, though when the disease was once established its victims fell easy prey to secondary infection. MacCallum stated that "there is no doubt whatever that this is a process in which injury to the arterial and venous walls is probably caused by some infectious agent." Allen and Lauderdale,[19] of the Mayo Clinic, stated that most students of thrombo-angiitis obliterans have been impressed by the probability that bacteria or their toxins are important etiologic factors in the genesis of the disease. They reported a case in which thrombo-angiitis obliterans was transferred from one human being to another. While amputating the toes of a man for thrombo-angiitis obliterans, a Scotch surgeon 45 years of age accidentally pierced the palmar surface of his hand and a finger with a spicule of bone from the patient's toe. A month later, changes in color, pallor and cyanosis were noted in the injured finger. Similar changes soon involved other fingers and left no doubt as to the accuracy of the diagnosis.

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[17] McGrath, E. J.: Experimental Peripheral Gangrene, J. A. M. A. **105:** 854-856 (Sept. 14) 1935.

[18] Buerger, L.: Is Thrombo-Angiitis Obliterans an Infectious Disease? Surg., Gynec. & Obst. **19:**582-588 (Nov.) 1914.

[19] Allen, E. V., and Lauderdale, T. L.: Accidental Transmission of Thrombo-Angiitis Obliterans from Man to Man, Proc. Staff Meet., Mayo Clin. **11:**641-644 (Oct. 7) 1936.

Many attempts have been made to reproduce the disease with infective agents. Saltikow inoculated animals with staphylococci, streptococci and tubercle bacilli, but the results were disappointing. Buerger in 1929 produced lesions similar to those of thrombo-angiitis obliterans by transplanting segments of veins affected with phlebitis migrans into human beings. Rabinowitz,[20] of Brooklyn, believed that he had found a certain gram-positive organism with which he could reproduce the disease, but his work was not convincing and received no support. Schmidt-Weyland,[21] of Königsberg, found that intravenous injections of highly virulent streptococci, tubercle bacilli of both human and bovine type and killed colon bacilli produced gangrene in rabbits' ears in 21 of 67 experiments, provided 0.5 cc. of a 1 : 1,000 solution of epinephrine hydrochloride was injected daily near the base of the rabbits' ears. Horton and Dorsey,[22] of the Mayo Clinic, have tried to reproduce thrombo-angiitis obliterans by implanting streptococci in the teeth of dogs. Likewise, numerous attempts have been made to culture the tissue of amputated limbs, but these have resulted in failure. These failures suggest either an inappropriate host or more likely failure to deal with the etiologic agent.

In a paper read before the New York County Medical Society on March 27, 1916, I [23] stated that for a number of years I had been much impressed with the remarkable latency of bacteria remaining in the body after infectious disease and the development of local foci set up by such bacteria long after the original infection had occurred. At that time I recalled that during a visit to Breslau in 1913 I was informed by two assistants of Professor Kuettner that they had found gangrene of the extremities to be frequent while they were doing medical service in the Bulgarian campaign. It occurred to me that in view of the great frequency of typhus and cholera in the Bulgarian camps there might be a causal relationship between these infections and the frequent occurrence of gangrene. In a conversation with Dr. Zinsser he informed me that during his visit to Serbia he had observed a considerable number of cases of gangrene of the extremities. Gangrene[24] is mentioned in a number of textbooks as a direct complication of typhus. It practically never occurs as a complication of cholera. A study of the epidemiology of typhus indicates that with the disease there is a coexistent high incidence of thrombo-angiitis obliterans. Starting with these facts, I developed my thesis, proposed in 1916, that typhus bears a definite etiologic relationship to thrombo-angiitis obliterans. In support of this thesis I am now prepared to submit the following data. I wish to expand the evidence for this relationship on epidemiologic, pathologic and experimental lines. It will be necessary first to describe both typhus and thrombo-angiitis obliterans.

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[20] Rabinowitz, H. M.: Experiments on the Infectious Origin of Thrombo-Angiitis Obliterans and the Isolation of a Specific Organism from the Blood Stream, Surg., Gynec. & Obst. **37:***353-360* (Sept.) 1923.

[21] Schmidt-Weyland, P.: Experimentelle Untersuchungen zur Erzeugung von Gangrän und ihre Beziehungen zur Thrombangiitis obliterans, Klin. Wchnschr. **11:**2148-2151 (Dec. 24) 1932.

[22] Horton, B. T., and Dorsey, A. H. E.: Experimental Thrombo-Angiitis Obliterans: Bacteriologic and Pathologic Studies, Arch. Path. **13:***910-925* (June) 1932.

[23] Goodman, C., and Bernstein, E. P.: Presenile Gangrene, Thrombo-angiitis Obliterans, New York M. J. **103:***1073-1074* (June 3) 1916.

TYPHUS

For centuries typhus has been coincident with the filth and squalor engendered of poverty and ignorance, as Hirsch's[25] oft repeated statement gives evidence: "The history of typhus is written in those dark pages of the World's story which tell of the grievous visitations of mankind by war, famine and misery of every kind."

Typhus has been described under various appellations: *tabardillo* in Mexico and *fièvre boutonneuse* in the French colonies of North Africa. Analogous diseases are Rocky Mountain spotted fever and Brill's disease, which are constantly present in the United States, and Japanese River fever and Manchurian fever. The vectors of endemic typhus are the rat flea and the rat louse, in contrast to epidemic typhus, in which the vector is the body louse.

A person who is undernourished, mentally fatigued or subjected to a great deal of privation and misery becomes the victim of infection more readily than one who is in better physical condition. The same applies to animals. Inoculate a rat the physical condition of which has not been reduced to a low state and it is not likely to yield as large a number of rickettsias as one that has been subjected to the devitalizing conditions.

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[24] Goodman, C.: Presenile Gangrene; Thromboangiitis Obliterans; Further Confirmation of Its Relation to Typhus Fever, M. Rec. 92:275-276 (Aug. 18) 1917.

[25] Hirsch, A.: Handbook of Geographical and Historical Pathology, translated by C. Creighton, London, New Sydenham Society, 1883.

Epidemic typhus was first recognized as a disease entity by Fracastorius [26] early in the sixteenth century, and Tobias Cober noted the relation of typhus to pediculosis in 1606. The disease has a widespread distribution, not only in tropical countries but in temperate and northern regions where the poor herd together in winter and where the body louse thrives and is spread.

The cause of typhus was unknown until 1911, when Ricketts succeeded in isolating the specific organism, known as Rickettsia Prowazeki. Ricketts demonstrated this organism in the blood of patients with typhus, while Prowazek in 1913 found it within the cells of the intestinal lining of typhus infected body lice. It can be transmitted to rats and guinea-pigs.

In 1931 Zinsser reported that he was able to produce an almost pure culture of Rickettsia by scraping the bodies from the tunica vaginalis of guinea-pigs which had been inoculated with the blood of patients with typhus. In 1934 Nigg [27] succeeded in growing Rickettsia, with living tissue as a medium, thereby proving beyond all doubt that rickettsia bodies are real organisms capable of cultivation. A vaccine of killed rickettsias, prepared by Zinsser and Ruiz Castaneda,[28] has produced protective immunity against both the European and the Mexican type of typhus.

Pathologic Picture.—Typhus is primarily a disease of the blood stream with rickettsias eventually embedded in the endothelial cells of the blood vessels. A number of investigators in foreign countries, including Wolff,[29] Wiener,[30] Fraenkel,[31] Jochmann [32] and others, as well as Wolbach [33] in this country, have stressed the fact that the infection often has a predilection for the intimal lining of the vessels of the extremities. Wiener, from postmortem examinations, concluded that the most characteristic pathologic evidence of typhus is the extreme fragility of the walls of the vessels. This may entail thrombotic formation in the vessels of the lower extremities and of other parts of the body.

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[26] Fracastorius, H.: De contagione, et contagiosis morbis, Venetiis, apud Juntas, 1574.

[27] Nigg, Clara: On the Preservation of Typhus Fever Rickettsia in Cultures, J. Exper. Med. **61**:17-26 (Jan.) 1935.

[28] Zinsser, H., and Ruiz Castaneda, M.: Studies on Typhus Fever: XII. The Passive Immunization of Guinea Pigs, Infected with European Virus, with Serum of a Horse Treated with Killed Rickettsia of the Mexican Type, J. Exper. Med. **59**:471-478 (April) 1934.

[29] Wolff, B.: Klinische und pathologisch-anatomische Beobachtungen beim Fleckfieber, Beitr. z. Klin. d. Infektionskr. **5**:1-74, 1916.

[30] Wiener, E.: Ueber Flecktyphus, Wien. klin. Wchnschr. **29**:117-119 (Jan 27) 1916.

[31] Fraenkel, E.: Zur Fleckfieberdiagnose, München. med. Wchnschr. **62**:805-808 (June 15) 1915.

[32] Jochmann, G.: Lehrbuch der Infektionskrankheiten, Berlin, Julius Springer, 1914, p. 757.

[33] Wolbach, S. B.; Todd, J. L., and Palfrey, E. M.: Etiology and Pathology of Typhus, Cambridge, Harvard University Press, 1922.

Fraenkel stated that the vascular lesions consist of cellular infiltration in the neighborhood of the arterioles. The outstanding study of the pathologic picture of typhus is that of Wolbach, who performed thirty-eight autopsies in unquestioned cases of typhus a few hours after death. He found a distinctive pathologic condition of the blood vessels, particularly those of the skin and the central nervous system. He wrote: "This lesion began as a proliferative reaction of the endothelium, followed by a thrombosis that may cause complete occlusion of the vessel."

Symptoms and Diagnosis.—Outspoken typhus is generally recognized by the principal symptoms, which are fever, extreme prostration and the lesions of the skin. An important factor from the standpoint of this thesis is that endemic forms and mild types of the disease occurring in epidemics are often overlooked. Nemschilov [34] stated that the disease is often devoid of symptoms or portrays only indefinite clinical signs, a fact that may be responsible for contagion and propagation. Brill and Baehr [35] wrote that mild abortive forms may occur in persons who have been exposed inordinately to infections and in whom there seems to be some degree of natural immunity. Clinically, it is difficult to diagnose the disease in the abortive form, and many times it is overlooked.

During an epidemic in Boston, Shattuck [36] wrote: "There are cases of socalled typhus fever without eruption in which the symptoms are mild and atypical."

Children particularly escape the severe forms of the disease during an epidemic, so that in later life a negative history of typhus does not indicate that a person has not been mildly infected.

In the diagnosis of typhus, the Weil-Felix agglutinative reaction with Proteus X19 is of value.

Isabolinski [37] and others, of the Statts Institute in Smolensk, U. S. S. R., found the Weil-Felix reaction to be strongly positive in 1 per cent of normal persons. They stated that the test was strongly corroborative but not 100 per cent positive and that it is rarely positive one year after typhus.

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[34] Nemschilov, S. F.: Ueber Hautreaktion mit Exanthin, Klin. Wchnschr. **13**:59-61 (Jan. 13) 1934.

[35] Brill, N. E., and Baehr, G.: Typhus Fever, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1927, vol. 1, chap. 10, pp. 190-201.

[36] Shattuck, G. C.: Typhus Fever in Boston and a Review of the Newer Methods of Diagnosing Typhus, Am. J. Trop. Med. **2**:225-250 (May) 1922.

[37] Isabolinski, M. P.; Sobolewa, R. M., and others: Zur Frage der epidemiologischen Bedeutung der Weil-Felix-Reaktion bei Flecktyphus, Ztschr. f. Immunitätsforsch. u. exper. Therap. **81**:405-409 (Feb. 15) 1934.

The exanthin reaction[38] with Proteus X19 filtrate injected intracutaneously has been used in the acute stage of the disease and is usually negative after the seventh day.

The results of another cutaneous test[39] in which formaldehydized rickettsia bodies were used were reported previously. These and further results will be reported in detail. Intracutaneous injections have caused reactions in patients who were convalescing from typhus as early as two weeks after the disease and in those who had recovered from typhus as late as several years after the disease.

Gangrene as a Complication.—Gangrene is preeminent among the many complications following typhus. During a tremendous epidemic which swept from Russia over the entire European Continent, resulting in millions of deaths, Thomas Jordanus (1576) observed that the cardinal symptoms of typhus are "high fever, prostration and *gangrene*." Similar observations were made during the nineteenth century by von Hildebrand,[40] Blümm,[41] Deppisch,[42] Graber,[43] Aspelin,[44] Gregory[45] and Kagan.[46]

It is interesting to note that during the Serbian campaign of 1913 and 1914 and during the World War medical journals and lay periodicals commented on the prevalence of gangrene among the troops. Exposure, chilling and frost-bite were held responsible. At the same time a similar condition was not reported from any other war areas where the climate was equally severe and the soldiers likewise suffered exposure. When this finding is taken into consideration in connection with the epidemic of typhus in southeastern Europe, it is highly suggestive of a relation between typhus and gangrene.

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[38] 38. Fleck, L., and Hescheles, I.: Ueber eine Fleckfieber-Hautreaktion (die Exanthinreaktion) und ihre Ähnlichkeit mit dem Dicktest, Klin. Wchnschr. **10**: 1075-1076 (June 6) 1931.

[39] 39. Goodman, C., and Brodie, M.: A Test for Diagnosis of Thrombo-Angiitis Obliterans, Proc. Soc. Exper. Biol. & Med. **32**:1331-1332 (May) 1935; Skin Test Indicating Previous Typhus Infection, ibid. **32**:1332-1334 (May) 1935. Goodman, C.: A Skin Test to Suggest the Diagnosis of Recovered Typhus and Thrombo-Angiitis Obliterans, Bull. New York Acad. Med. **11**:403-405 (June) 1935.

[40] 40. von Hildebrand, J. V.: Ueber den ansteckenden Typhus, Vienna, Camesina, 1815.

[41] 41. Blümm, H.: Ueber Gangrän nach Typhus, Inaug. Dissert., Würzburg, C. J. Becker, 1872.

[42] 42. Deppisch, A.: De gangræna typhum subsequente, Inaug. Dissert., Dorpat, H. Laakmanni, 1852.

[43] 43. Graber, C.: Gangrän der Extremitäten nach Typhus, Inaug. Dissert., Breslau, H. Lindner, 1869.

[44] 44. Aspelin, E. F.: Om gangrän uti nedra extremiteterna efter tyfus, Inaug. Dissert., Helsingfors, J. C. Frenckell & Son, 1868.

[45] 45. Gregory, A.: Chirurgische Erkrankungen als Komplikation nach Typhus exanthematicus und recurrens, Deutsche Ztschr. f. Chir. **181**:66-73, 1923.

[46] 46. Kagan, S.: Gangrene of the Foot as a Complication of Typhus Fever and Its Treatment, Boston M. & S. J. **189**:593-594 (Oct. 25) 1923.

THROMBO-ANGIITIS OBLITERANS

Presenile gangrene is a vascular disease of young or middle-aged males, usually occurring in the extremities. The chief complaint is intermittent claudication. On examination there is usually diminution or absence of pulsation in one or more of the tibial arteries. and the temperature of the limb is lower than that of the unaffected extremity.

Sex.—Thrombo-angiitis obliterans is predominantly a disease of the male sex. McGrath[17] and others have attempted to account for this on the ground that the "female sex hormones" afford protection against the disease. It is well to remember, however, that both typhus and Brill's disease are particularly common among males. Brill's disease is most frequently found among workers in graineries and ports, where rats are found in large numbers and naturally the rat flea and the rat louse abound. Typhus is common in armies and prisons, where the population is largely male. Friedman mentioned as a reason why women are less often victims of thrombo-angiitis the fact that they lead more or less protected lives, while men are constantly exposed to infection of all kinds. The disease does occasionally occur in women. Trabaud and Mredden[47] reported the case of an Arabian girl, aged 20. in whom both feet and both hands were affected.

About forty years ago, as an intern at the Mount Sinai Hospital. I saw my first case of thrombo-angiitis obliterans, at a time when the disease was first appearing coincident with the arrival of numerous immigrants from Russia and central Europe. The disease was eventually recognized as that described by Winiwärter,[48] of Billroth's Clinic, in 1879 under the name of endarteritis obliterans.

Pathologic Picture.—Buerger's description is much like that of Winiwärter, who wrote that in the arteries proliferation of the intima occurs with the narrowing of the lumen; there is a coagulation of the blood with thrombotic formation, which becomes organized. Infiltration of the media appears later. Proliferation may be patchy and may not involve the entire circumference. New capillaries appear, with round cell infiltration of the media. The veins likewise show proliferation and elevations about the valves, infiltration extending to the media and adventitia and new capillary formation in the thrombus corresponding to canalization.

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[47] Trabaud, J., and Mredden: Maladie de Léo Buerger chez une jeune fille musulmane, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:579-583 (April 6) 1931.

[48] Winiwärter, F.: Ueber eine eigenthümliche Form von Endarteriitis und Endophlebitis mit Gangrän des Fusses, Arch. f. klin. Chir. **23**:202-226, 1879.

Buerger, who considered the term "thrombo-angiitis obliterans" a more accurate description of the condition, summarized his findings in these words:

> Most of the large arteries and sometimes the veins as well are obliterated over a large extent of their course. All stages in the occlusive change may occur in the various vessels of the extremity or in the same vessel in the different parts of its course. The closure of the vessel is affected by red obturating thrombi. These become organized, vascularized and canalized. Recent red thrombi may involve large portions of the arteries or veins and are not secondary to the gangrenous process. They may occur even when no gangrene is present. In short, we are dealing with lesions of considerable extent, apparently initiated by the formation of occlusive thrombi, chiefly in the arteries, but not confined to these, followed by organization and healing with an attempt at the production of sufficient collateral circulation.

My own observations on the living subject have been in accord with those of Buerger only so far as the type of lesion is concerned but not as to distribution. In a series of 17 cases of arteriovenous anastomoses in which surgical treatment was employed, I[49] found the femoral artery invariably more or less thickened and in several instances almost completely occluded, whereas the femoral vein, while showing some thickening of its wall, always retained its lumen.

It is a well established fact that presenile gangrene is a vascular constitutional disease, although it most frequently manifests itself in the vessels of the lower extremities. It is accepted that vascular complication arising in the course of other diseases, such as arteriosclerosis and diabetes, also manifests itself mainly in the lower extremities as a rule. In 1932 Jäger,[50] of Leipzig, published an article in which he describes the autopsy observations in 8 cases in which he found thrombo-angiitis obliterans in vessels other than those of the lower extremities. Taube,[51] of New York, described 2 cases in which he discovered the disease in the vessels of the abdomen. Cohen and Barron (1936) compiled from the literature reports of 15 cases of thrombo-angiitis obliterans suggesting involvement of the vessels of the alimentary tract. Only 4 of these were proved at autopsy. These authors presented an additional presumptive case.

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[49] Goodman, Charles: Arterio-Venous Anastomosis for *Impending Gangrene: A Report of Personal Experience with Fifteen Operated Cases*, Tr. Internat. Cong. Med., London (sect. VII, pt. 2, Surg.), 1913, pp. 101-123.

[50] Jäger, E.: Zur pathologischen Anatomie der Thrombangiitis obliterans bei juveniler Extremitätengangrän, Virchows Arch. f. path. Anat. **284**:526-622, 1932.

[51] Taube, N.: Mesenteric Involvement in Buerger's Disease (Thrombo-Angiitis Obliterans): Report of Two Cases, J. A. M. A. **96**:1469-1472 (May 2 1931.

Perla,[52] Dürck,[53] Lemann[54] and others reported finding thrombo-angiitis obliterans in the coronary artery. Recently Saphir[55] reported the results of postmortem examinations of the coronary arteries in a series of 30 cases of thrombo-angiitis obliterans collected from the literature. Lemann, who in 1928 described a similar case, emphasized the frequency with which coronary involvement occurs in this disease. Birnbaum, Prinzmetal and Connor[56] described a case of generalized thrombo-angiitis obliterans with involvement of the retinal vessels and adrenal infarction.

RELATIONSHIP OF TYPHUS TO THROMBO-ANGIITIS OBLITERANS

Epidemiologic Relation.—In considering the European environment. one fact stood out most conspicuously, namely, that typhus was constantly endemic and frequently epidemic in Russia and in certain mid-European areas. It was practically pandemic in the crowded Jewish quarters. In Russia the incidence of typhus, both virulent and mild, is high, while the incidence of thrombo-angiitis obliterans is also high.

Typhus is endemic in Russia, Siberia, Central Europe, Ireland and North Africa, in South America, especially in Chili and Peru, and in the United States, where it is known as Brill's disease. About 2,000 cases are reported annually in the United States. Likewise, thrombo-angiitis occurs in these areas.

Studies of Zinsser in New York indicate a close parallel between the incidence of thrombo-angiitis obliterans and that of typhus. From 1910 to 1933, of all the cases of typhus recorded in New York 97 per cent were in Jews, and 92.3 per cent of the afflicted Jews were of foreign birth. During the period 1921 to 1933, when a considerable portion of the total Jewish population of New York was of native birth, 91 per cent of all cases were in Jews, 85 per cent of whom were of foreign birth. Of the total of 538 cases of typhus occurring in New York and Boston during a thirty year period, 94.8 per cent were in persons of foreign birth. Of all the cases. over 97 per cent were in the Jewish racial group, and within this group 95 per cent were in the foreign-born members. The large percentage of Jews in these statistics merely means that the immigrants from typhus endemic areas to the United States consisted largely of Jews and the large percentage of Russians means almost entirely Russian Jews.

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[52] Perla, D.: An Analysis of Forty-One Cases of Thrombo-Angiitis Obliterans, with a Report of a Case Involving the Coronaries and the Aorta, Surg., Gynec. & Obst. **41**:21-30 (July) 1925.

[53] Dürck, H.: Die sogenannte "Thrombangiitis obliterans" im Rahmen der infektiös-toxischen Gefässentzündungen, Verhandl. d. deutsch. path. Gesellsch. **25**: 272-289 (April) 1930.

[54] Lemann, I. I.: Coronary Occlusion in Buerger's Disease (Thrombo-Angiitis Obliterans), Am. J. M. Sc. **176**:807-812 (Dec.) 1928.

[55] Saphir, O.: Thromboangiitis Obliterans of the Coronary Arteries and Its Relation to Arteriosclerosis, Am. Heart J. **12**:521-535 (Nov.) 1936.

[56] Birnhaum, W.; Prinzmetal, M., and Connor, C. L.: Generalized Thrombo-Angiitis Obliterans: Report of a Case with Involvement of Retinal Vessels and Suprarenal Involvement, Arch. Int. Med. **53**:410-422 (March) 1934.

On the basis of these figures it might well be assumed that typhus, had it not been a well known disease with a world-wide incidence, might, like thrombo-angiitis obliterans, have been described as a predominantly Jewish disease. The fact that during the same period and in the same city the two diseases appeared almost simultaneously and almost exclusively in a racial group coming directly from the typhus centers of Russia and Central Europe is highly significant.

Both diseases have quiescent periods, and there may be recrudescences. Outbreaks of typhus vary considerably in virulence. Some infections gradually lose their virulence and finally disappear for an indefinite period or pass unrecognized. They then reappear in an intensely virulent form. This is particularly true when an infectious disease has prevailed for a great many years and the inhabitants have become more or less immune or when, as has been suggested, exposure to the disease has resulted in a very mild or unapparent form of the disease, which affords protective immunity.

Both diseases give rise to endothelial changes and thrombosis, with infiltration about the walls of the vessels.

In 1917 I attempted to reproduce the disease in guinea-pigs with injections of blood from patients with typhus. Microscopic study of the vessels of the hindlegs showed changes analogous to those seen in thrombo-angiitis obliterans.

In 1922 Wolbach published an exhaustive monograph of his studies on typhus in Poland. He mentioned thrombosis engendered by the presence of rickettsias in the endothelium. At that time I had under my care a number of patients with gangrene in the advanced stage which necessitated amputation. I prevailed on Dr. Klein, the pathologist of the Montefiore Hospital, to look for rickettsia-like bodies in the vessels which I had dissected from the amputated limbs. He reported that he found bodies like those described by Wolbach, but he did not attempt to grow them because no method for tissue culture existed at that time. Dr. Seecof, working independently and without the knowledge of Dr. Klein's findings, also discovered bodies which resembled Wolbach's microscopic picture of Rickettsia in material from thrombo-angiitis obliterans patients.

EXPERIMENTAL WORK AND RESULTS

The recent studies of Zinsser concerning the possible relationship of Brill's disease to a previous typhus infection suggests the importance of determining by a simple test a previous infection with typhus. We proceeded, therefore, to attempt to establish further identity between the two conditions by a cutaneous test.

The purpose of the test is to determine: (1) whether with a formaldehydized preparation of rickettsia bodies a reaction can be observed in persons who have recovered from typhus; (2) whether cutaneous reactions can be obtained in persons with thrombo-angiitis obliterans, and (3) whether any cutaneous reaction obtained is quantitative or qualitative.

A few efforts have been made by others to devise a cutaneous test. For example, Jacobsthal[57] in 1916 made a louse extract from typhus-infected lice in which the virus was killed. Intracutaneous inoculation gave a positive reaction in patients with acute typhus, but the procedure was entirely too complicated to be of practical value. Friedberger, Sparrow and Delanoë used a small amount of Proteus X19, but this test gave a positive reaction in cases of typhoid and relapsing fever as well and hence was of little diagnostic value. Bogdanoff,[58] Fleck and Krukowsky devised a modified exanthin test which they claimed was specific for typhus during the first week. In the convalescent period the reactions of 80 per cent of the patients became negative, and positive results were observed in healthy persons. This reaction, therefore, could not take the place of the Weil-Felix reaction.

In several former publications I have described the test which I devised, using a formaldehydized vaccine supplied through the courtesy of Dr. Hans Zinsser, of the Department of Bacteriology and Immunology of the Harvard University.

Technic for Cutaneous Test.—The technic consists of an intracutaneous injection of from 0.1 to 0.2 cc. of the vaccine on the palmar aspect of the forearm. For control tests, Proteus X19 filtrate and a formaldehydized suspension of tunica vaginalis from healthy guinea-pigs were used as well as a suspension of streptococci and staphylococci.

For these tests three groups of persons were selected: (1) patients with thrombo-angiitis obliterans, (2) persons convalescent and recovered from typhus and Brill's disease and (3) normal persons.

EXPERIMENT 1.—The first group tested consisted of 20 patients. The results, which have already been reported, are as follows: All of these patients had a history of Brill's disease from six to eight years previously, and in all but 1 case the diagnosis at that time had been confirmed by the Weil-Felix reaction. For controls, 22 adults with no previous history of typhus were given similar tests with the suspension of rickettsia. These patients were observed for from twenty-four to forty-eight hours after the injections were given. The results are given in table 1. None of the 22 controls gave any reaction, whereas all of the 20 with a history of previous typhus infection showed an erythematous indurated area from 1 to 4 cm. in diameter at the end of twenty-four hours. Another person similarly tested two weeks after convalescence likewise had a reaction 2 cm. in diameter.

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[57] Jacobsthal, E.: Eine Anregung zur Anstellung von Kutisreaktion bei Fleckfieber, Deutsche med. Wchnschr. **42**:1093-1094 (Sept. 7) 1916.

[58] Bogdanoff, I. L.: Ueber eine intrakutane Reaktion beim Flecktyphus, Zentralbl. f. Bakt. (Abt. 1) **128**:173-177 (April 28) 1933.

These results suggest that patients who have recovered from typhus display a sensitivity to rickettsia bodies and that this sensitivity persists for a considerable period of time.

Experiment 2.—In a second group of 32 adults with thrombo-angiitis obliterans, some with and others without gangrene, the tests with a formaldehydized suspension of rickettsia were similarly made. These showed without exception a 1 plus or a 2 plus reaction. (An erythematous area from 0.5 to 2 cm. in diameter was recorded as 1 plus, and anything larger was recorded as 2 plus.) For control tests, Proteus X19 filtrate was used on 9 of these patients, a suspension of tunica vaginalis from healthy guinea-pigs on 9 and a suspension of staphylococci and a suspension of streptococci on 9 and 6, respectively. All of the patients showed a negative reaction, with the exception of those having ulceration or gangrene. In 1 of the patients in the latter group the reaction to the streptococcus vaccine was positive, while in 4 the reaction to the staphylococcus vaccine was positive.

Table 1.—*Results in Experiment 1*

Subjects	Number of Persons	Reaction to Suspension of Rickettsia (Zinsser No.1)	Reaction to Proteus X19 Filtrate	Reaction to Suspension of Tunica Vaginalis
Persons recovered from typhus..	20	20+	20—	20—
Control subjects................	22	22—	22—	22—

A series of 11 adults with arteriosclerosis and others with diabetes, some with and others without gangrene, responded negatively both to tests with rickettsias and to control tests, excepting 2 with gangrene in whom the cutaneous reaction to the staphylococcus vaccine was positive.

Preparation of Vaccines.—At this time preparation for the production of vaccine in the laboratory of the New York University was undertaken. This was made possible through the courtesy of Dr. W. H. Park.

These vaccines were prepared according to Dr. Zinsser's technic and carried out with the assistance of Mr. George J. Stein. We inoculated guinea-pigs and rats passed through several generations in order to obtain the maximum number of rickettsias.

Material for the initial inoculations was derived from a tissue culture strain furnished us through the courtesy of Dr. Landsteiner, of the Rockefeller Institute, as well as from guinea-pigs inoculated with Mexican typhus furnished us by Dr. Zinsser. Another European tissue culture furnished us by Dr. Landsteiner was passed through several generations of pigs, and a brain emulsion was prepared To this group of Mexican typhus vaccine and the European virus, we were able to add a European typhus vaccine prepared for me by Professor Weigl, of Poland.

Mexican Typhus Vaccine.—With the cooperation of Dr. Ira I. Kaplan, of the Bellevue Hospital, rats were irradiated with a dose of 700 roentgens and immediately inoculated intraperitoneally with an emulsion of tunica vaginalis from guinea-pigs infected with Mexican typhus. Five days after inoculation each rat was killed by a blow on the head, dipped in compound solution of cresol to kill all lice, shaved and put on a board. The peritoneal lining and tunica vaginalis were removed. These were washed several times in sodium citrate to which a 0.2 per cent concentration of solution of formaldehyde U. S. P. had been added. They were pooled and washed again several times. They were then centrifugated fractionally. The residue was ground with sand and centrifugated again and again until purified and rendered free as possible from cellular detritus.

We then received a third supply of vaccine from Dr. Zinsser. At first the results with this vaccine were disappointing as we observed reactions in presumably normal persons. Experiments were therefore undertaken to determine the reason.

Experiment 3.—The vaccine was heated for thirty minutes at 70 C. in a water bath. The results were not encouraging.

Table 2.—*Results with N. Y. U. Vaccine 1, 2 and 3* *

Subjects	N. Y. U. 1	N. Y. U. 1 Heated	N. Y. U. 1 (120,000,000 to 170,000,000)	N. Y. U. 2 (150,000,000)	N. Y. U. 3 (150,000,000)
Persons with thrombo-angiitis obliterans	7+ 1—	1+ 1—	61+ 1—	20+ 2—	14+
Control subjects.................	8— 1+	7— 7+	16— 3+	18— 1+	5—

* N. Y. U. vaccine refers to the vaccine prepared in the laboratory of New York University.

Table 3.—*Comparative Results with Weigl and with N. Y. U. Vaccine*

Subjects	Weigl (140,000,000)	N. Y. U. 1 (120,000,000 to 150,000,000)	N. Y. U. 2 (140,000,000 to 150,000,000)	N. Y. U. 3 (140,000,000 to 150,000,000)
Persons with thrombo-angiitis obliterans	26+ 100%	37+ 97% 1— 3%	20+ 91% 2— 9%	14+ 100%
Control subjects............................	14— 100%	8— 100%	18— 95% 1+ 5%	5— 100%

Experiments 4, 5, 6 and 7.—Tests were carried out with dilutions 1:4, 1:6, 1:7 and 1:10, respectively. With the higher dilutions, the reactions proved more consistently uniform in patients with typhus and in those with thrombo-angiitis and negative in the controls.

Experiments 8, 9 and 10.—Similar tests were made with dilutions of vaccine with batches 4, 5 and 6 prepared in our laboratory and carried out after the preliminary results with the third batch of vaccine from Dr. Zinsser.

Results with these various vaccines at our command indicated that each product must vary in the quantity of its essential ingredient. It became evident that a standardized preparation was necessary to render the tests of practical value.

The streptococci and staphylococci used for our control test had been labeled at their source and identified by the number of bacteria contained in each cubic centimeter. It occurred to me, therefore, to apply the same principle for our rickettsia vaccines. The vaccines prepared by us as well as that obtained from Dr. Zinsser and the European strains made from typhus-infected lice furnished us by Professor Weigl were titered. We made use of the standardization measure of counting against normal red blood cells. We found that the batches of vaccine varied considerably in the number of rickettsias contained, namely, from 828,000,000 to 2,200,000,000 rickettsias to a cubic centimeter. The emulsion of the brains of guinea-pigs prepared from the European culture obtained from Dr. Landsteiner did not lend itself to titrating.

TABLE 4.—*Experiments and Results with Eight Different Batches of Vaccine and Control Tests*

	Persons with Thrombo-angiitis Obliterans	Persons with Typhus	Control Subjects
Zinsser No. 1	12+	25+	13— 1+
Zinsser No. 2	21+	13+	3—
Zinsser No. 3	9+ 1—	13+ 2—	2— 2+
Zinsser No. 3 (heated)	5+	1+	
Zinsser No. 3, 1:4	9+ 2—	9+ 2—	5— 1+
Zinsser No. 3, 1:4 (heated)	11+ 4—	15+ 6—	24— 2+
Zinsser No. 3, 1:10	7+ 8—	3+ 4—	7— 1+
Zinsser No. 3 (140,000,000)	....	4+ 1—	
Proteus X19 filtrate	5—	5—	3—
Tunica vaginalis	19—	22—	7—
Weigl	12+ 2—	12+ 2—	
Weigl (heated)	1+	1+	3— 1+
Weigl, 1:4	11+ 4—	17+ 4—	10— 3+
Weigl, 1:4 (heated)	23+ 4—	24+ 5—	14— 2+
Weigl (140,000,000)	26+	9+ 1—	17—
N. Y. U. 1	7+ 1—	2+	8— 1+
N. Y. U. 1 (heated)	1+ 1—	2+ 1—	7— 7+
N. Y. U. (170,000,000)	34+ 3—	47+ 1—	4— 2+
N. Y. U. (150,000,000)	12+	3+	1+
N. Y. U. (120,000,000)	25+ 1—	28+ 3—	8—
N. Y. U. (100,000,000)	5+ 5—	1+ 2—	4—
N. Y. U. 2	6+ 2—	2+	6—
N. Y. U. (150,000,000)	8+ 1—	6+	12— 1+
N. Y. U. (140,000,000)	12+ 1—	33+ 1—	
N. Y. U. (100,000,000)	3+ 2—	2—	
N. Y. U. 3	....	....	....
N. Y. U. (150,000,000)	8+	4+ 1—	5—
N. Y. U. (140,000,000)	6+	10+ 6—	
N. Y. U. (100,000,000)	1+		
N. Y. U. European vaccine 1:10	3+ 1—	1—	7—
Staphylococci	5+ 7—	3+ 4—	8— 3+
Streptococci	9+ 7—	5+ 4—	9—
N. Y. U. 1, 2 and 3 (pooled)	....	4+	2—

In the course of our experiments we have made over 600 intradermal tests with suspensions of Rickettsia Prowazeki and control material in the following subjects: 96 patients convalescing or recovered from Brill's disease (or typhus); 94 patients with thrombo-angiitis, and over 100 controls.[58a] These controls included a series of presumably normal persons and persons with arteriosclerosis, diabetes, typhoid, pneumonia, scarlet fever, bacterial endocarditis, intestinal tuberculosis and other acute infectious conditions.

[58a] These tests were made possible through the cooperation of the staff of the Brooklyn Jewish Hospital.

We found that an intracutaneous injection of 0.1 cc. of suspension containing approximately 150,000,000 rickettsias per cubic centimeter will be followed in cases of thrombo-angiitis obliterans by a reaction demonstrated within twenty-four hours by an erythematous area from 0.5 to 4 cm. in diameter. This usually disappears in the course of another twenty-four hours. In our series of controls these tests proved almost invariably negative. The summary of the results with the various preparations and their dilutions is given in the tables. Of interest was the observation in the course of our examination of the series of patients with Brill's disease. A considerable number of those complained of persistent and frequent headache as well as pains in the lower extremities, including intermittent claudication. Among these, there came to our notice 11 persons with a history of at least two attacks of typhus with an interval of several years, as well as one who had had typhus no less than three times. An examination of the extremities of these persons disclosed absence of pulsation in one or more of the tibial arteries with an appreciable difference in the amplitude of one extremity as compared with the other, as demonstrated by the oscillometer. These patients portrayed subjective and objective findings suggestive of thrombo-angiitis obliterans. Several of them gave a history of never having smoked or used tobacco.

COMMENT

Since I was first impressed in 1916 by the possible etiologic relationship of typhus to thrombo-angiitis obliterans, the same idea has suggested itself to Netter,[59] in 1932. Similar opinions have been expressed by Troisier and Horowitz,[60] who reported a case in which the Weil-Felix reaction was intensely positive in a 23 year old man with Buerger's disease, while in 7 controls the reaction was negative. Angelescu, Georgescu and Buzoianu,[61] on the basis of observations made in Roumania, stated that they have been impressed by the possibility that exanthematous typhus may be a factor in the production of chronic obliterating arteritis.

From the foregoing review, the test outlined, the epidemiologic evidence, the pathologic similarity and the facts that in a considerable proportion of patients with typhus clinical evidence of thrombo-angiitis obliterans develops and that the cutaneous test is positive in persons with typhus as well as in persons with thrombo-angiitis obliterans, it appears that there is a relation between the two diseases.

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[59] Netter, A.: Nécessité de la recherche des manifestations inapparentes du typhus endémique chez les matelots des équipages de Toulon, Bull. Acad. de méd., Paris **107**:156-158 (Feb. 9) 1932.

[60] Troisier, J., and Horowitz, A.: Maladie de Buerger et typhus exanthématique, Bull. et mém. Soc. méd. d. hôp. de Paris **57**:151-157 (Feb. 3) 1933.

[61] Angelescu, C.; Georgescu, G., and Buzoianu, G. V.: Exanthematous Typhus as an Etiologic Factor in Chronic Arteriitis Obliterans, Spitalul **50**:401-402 (Nov.) 1930.

SUMMARY

Of the various agents that have been suspected of having an etiologic relation to thrombo-angiitis obliterans, none have thus far given any substantial evidence to support the suspicion. Thrombo-angiitis obliterans is a disease not confined to any one race or locality. Like typhus and the typhus-like fevers, its occurrence is widespread.

A study of the epidemiology of these diseases shows that where one of them is common the other is also abundant. Gangrene of the extremities is an outstanding complication of typhus, being a more frequent sequela of typhus than any other infection. Those who have made a thorough study of thrombo-angiitis obliterans agree that it is a constitutional disease of infectious origin. On the basis of these facts I developed the thesis that typhus bears a definite etiologic relation to thrombo-angiitis obliterans. In support of this thesis I present certain highly suggestive evidence. I first devised a cutaneous test which gives a positive reaction over a prolonged period in persons who have had typhus. This test is almost uniformly positive in persons who have had typhus or Brill's disease and almost uniformly negative in normal persons. In a group of adults with thrombo-angiitis obliterans the test was almost uniformly positive, while in a group with arteriosclerosis and diabetes it was negative.

The findings in these series of tests are highly suggestive of an etiologic relation between typhus and thrombo-angiitis obliterans. They open the way for further research, and they justify the hope that eventually an immunologic agent may be found which will inhibit the development of thrombo-angiitis obliterans.

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ALTERATIONS IN THE HIP JOINT AFTER DEAFFERENTATION

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In studying the effect of lumbar sympathectomy and section of the lumbosacral dorsal roots on the structure of bones and joints in adult cats, a condition closely simulating the arthritic changes in malum coxae senilis of man was found in deafferented hip joints.

The numerous experimental procedures on animals, such as the rabbit, dog, cat and guinea-pig, which have resulted in conditions simulating arthritis deformans in man were reviewed by Burckhardt,[1] Mannheim [2] and Key.[3] These experiments usually included intracapsular traumatization or destruction of a portion of the articular cartilage and resulted in the acceptance by many of the thesis that degeneration of articular cartilage is a primary condition in the production of the senile type of chronic hypertrophic arthritis in man. Axhausen [4] has been the foremost exponent of this concept. From his experimental work on dogs, Wollenberg [5] concluded that degenerative alterations in a joint are primarily due to changes in the blood supply to that joint and that atrophic and hypertrophic changes may be explained on the basis of localized ischemia and hyperemia, respectively. On the other

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From the Department of Anatomy, Stanford University.

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1. Burckhardt, H.: Experimentelle Untersuchungen über die Beziehungen der Gelenkfunktion zur Arthritis deformans, Arch. f. klin. Chir. **132**:706, 1924.

2. Mannheim, A.: Experimentelle Arthritis deformans, Arch. f. klin. Chir. **156**:334, 1930.

3. Key, J. A.: Experimental Arthritis, Chronic and Atrophic, M. J. & Rec. **138**:369 (Nov. 15) 1933.

4. Axhausen, G.: Kritisches und Experimentelles zur Genese der Arthritis deformans, insbesondere über die Bedeutung der aseptischen Knochen- und Knorpelnekrose, Arch. f. klin. Chir. **94**:331, 1911; Ueber einfache, aseptische Knochen- und Knorpelnekrose, Chondritis dissecans und Arthritis deformans, ibid. **99**:519, 1912; Neue Untersuchungen über die Rolle der Knorpelnekrose in der Pathogenese der Arthritis deformans, ibid. **104**:301, 1914.

5. Wollenberg, G. A.: Aetiologie der Arthritis deformans, Ztschr. f. orthop Chir. **24**:359, 1909.

hand, Lane[6] attributed such changes to pressure, while Meyer[7] emphasizes the fact that certain changes in the joints in man may result from trauma of use and that synovial bursae, articular cartilages, capsules and tendons frequently show changes which suggest that they were produced solely by attrition in otherwise normal joints. It is interesting that Virchow and Fränkel[8] in considering changes in the joints in tabes dorsalis and arthritis deformans attributed the defects in the cartilage and bony polishing to the mechanical trauma of friction, but never on intact normal cartilage, always on hyperplastic softened cartilage.

In attempting to determine the pathogenesis of Charcot joints, Eloesser[9] sectioned the lumbosacral dorsal roots in a large series of cats. In active animals which used their deafferented limbs considerably he found changes in the joints that were highly characteristic of those seen in the neuropathic arthropathies. He concluded that the cause of these deformed joints was altered function, due to insensibility of the joints.

MATERIAL AND METHODS

In the experiments reported here, fifteen cats were used. The lumbar sympathetic chain was excised bilaterally in seven animals and unilaterally in eight. The fourth, fifth, sixth and seventh lumbar dorsal roots and the first, second and third sacral dorsal roots were also sectioned unilaterally on the side of the sympathectomy, in four of the cats before and in nine after, sympathectomy. In two of the animals unilateral sympathectomy was not followed by deafferentation. The interval between these operations varied from two weeks to one year; that between sympathectomy and autopsy varied from one hundred and twenty-seven to one thousand and ninety-seven days, and that between deafferentation and autopsy, from fourteen to one thousand, one hundred and fifty-eight days.

Ether anesthesia was used in all of the operative procedures, and the animals were watched carefully to prevent the development of traumatic ulcers of the skin. Ten of the cats were permitted to run freely in a large outdoor cage, about 8 by 10 feet (2.4 by 3 meters), and five were kept in relatively small standard animal cages, 1½ by 2 feet (0.45 by 0.6 meter). As will be seen later, this difference in the range of activity undoubtedly played a part in the absence or presence of the articular changes.

Roentgenograms were made of the entire lower extremity of each animal before autopsy and after fixation and cleaning of the bones. Careful macroscopic and microscopic examinations of the bones were made after fixation in diluted solution of formaldehyde U. S. P. (1:10), the histologic studies being made on bones decalcified in a 5 per cent aqueous solution of nitric acid and embedded in pyroxylin. The craniocaudal and dorsoventral diameters of the heads of the femurs were measured. The femurs, patellae, tibias and fibulas of five animals were cleaned of all soft parts, dried in the oven at 110 C., then placed in a number of changes of ether to remove the fat and again dried at 110 C. until a constant weight was obtained. In all animals the normally innervated limb or its component parts served as a control.

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[6] Lane, W. A.: The Causation and Pathology of the So-Called Disease Rheumatoid Arthritis, and of Senile Changes, Tr. Path. Soc. London **37**:387, 1886.

[7] Meyer, A. W.: Further Observations upon Use-Destruction in Joints, J. Bone & Joint Surg. **4**:491, 1922; Evidences of Attrition in the Human Body, Anat. Rec. **25**:142, 1923; Further Evidences of Attrition in the Human Body, Am. J. Anat. **34**:241, 1924; The Minuter Anatomy of Attrition Lesions, J. Bone & Joint Surg. **13**:341, 1931.

[8] Virchow, R., and Fränkel, B.: Berliner medicinische Gesellschaft, Berl. klin. Wchnschr. **23**:851, 1886.

[9] Eloesser, L.: On the Nature of Neuropathic Affections of the Joints, Ann. Surg. **66**:201, 1917.

RESULTS

The bones and joints of the two animals on which lumbar sympathectomy only was performed showed no changes after two years, but the hip joints of animals which used their deafferented limbs considerably showed alterations. Except for the slight increase in the weight of the bones in the deafferented limbs (table 1) and the changes in the hip joints, no alterations were noticed in the denervated bones. It is significant that the increase in weight in the affected bones roughly paralleled the extent of the deformation.

TABLE 1.—*Weight of Bones After Drying and Extraction with Ether*

Cat	Days Separating Operation and Autopsy		Bones	Weight of Bone on Normal Side, Gm.	Weight of Bone on Side Operated On, Gm.	Difference, Gm.
	Sympathectomy	Deafferentation				
238	1,029	728	Femur	7.02	7.84	+0.82
			Patella	0.33	0.34	+0.01
			Tibia	6.60	7.20	+0.60
			Fibula	0.89	0.87	—0.02
421	379	350	Femur	6.50	6.97	+0.47
			Patella	0.27	0.26	—0.01
			Tibia	5.44	5.43	—0.01
			Fibula	0.72	0.95	+0.23
276	672	1,009	Patella	0.29	0.32	+0.03
			Tibia	6.87	7.36	+0.49
			Fibula	0.88	1.10	+0.22
277	734	1,008	Patella	0.54	0.52	—0.02
			Tibia	9.90	10.00	+0.10
			Fibula	1.22	1.24	+0.02

The manner in which the deafferented hindlimb was carried is illustrated in figure 1. It was extended at the hip and knee, the dorsum of the foot dragging along the ground. Although the cat shown in figure 1 carried the left hindlimb in an abducted position, most of the cats carried it in adduction. The deafferented limb offers less support than the normal limb, causing the pelvis to tilt toward the denervated side and bringing that leg into adduction. Adduction and abduction increase tension on the upper and lower portions, respectively, of the capsule, which if prolonged permits an increase in the range of movement of the joint. This hypermobility permits excessive wear on portions of the articular surface unadapted to it, in joints the proprioceptive sense of which has been abolished, and prevents maintenance of the normal position.

The roentgenogram of the hind part of a cat on which deafferentation was performed one thousand, one hundred and fifty-eight days previously and sympathectomy seven hundred and thirty-six days previously is shown in figure 2. Subluxation of the head of the femur toward the iliac surface is present on the left. The acetabular fossa appears very shallow, and an increase in the density of the spongiosa of the head and neck of the femur is indicated. This increase in density extends even into the cortex of the bone. The change in the head of the femur is more apparent in figure 3, which is a roentgenogram of the fresh stripped bones of the hindlimbs of the cat shown in figure 2, but reversed in position. There are marked increase in density, flattening of the weight bearing portion and an increase in the diameter of the head of the femur.

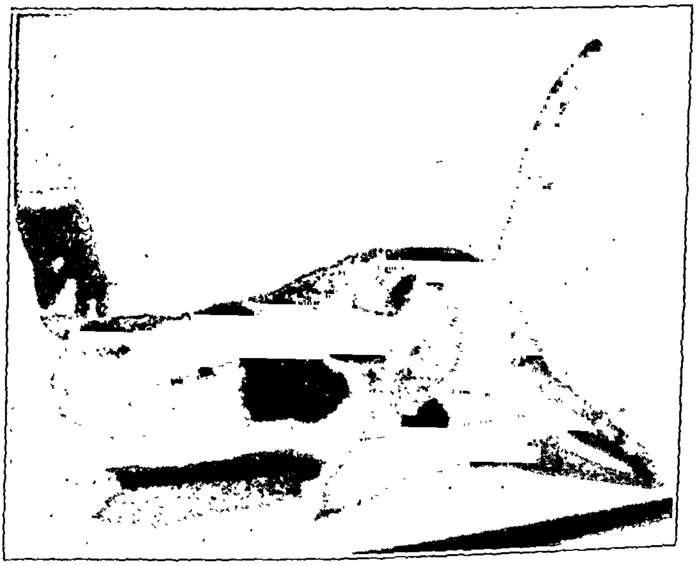

Fig. 1.—Photograph of cat 238 showing extension and abduction of the deafferented (seven hundred and twenty-eight days) and sympathectomized (one thousand and twenty-nine days) hindlimb. The dorsum of the foot is dragging on the ground.

The weights of the dried femurs, patellae, tibias and fibulas of four of the cats are given in table 1. Marked arthritic changes were found in the hip joint of cat 238. The femur and the tibia of the deafferented limb were heavier than those of the normal limb, the difference in weight being greater than those between the bones in deafferented limbs of animals without alterations in the hip joints. It is surprising that this increase in weight was present also in the deafferented tibias. The femurs on the sides with marked changes in the hip joints always were slightly heavier than those from the normally innervated limbs when weighed devoid of soft parts but without drying. The bones used for microscopic study could, of course, not be subjected to drying.

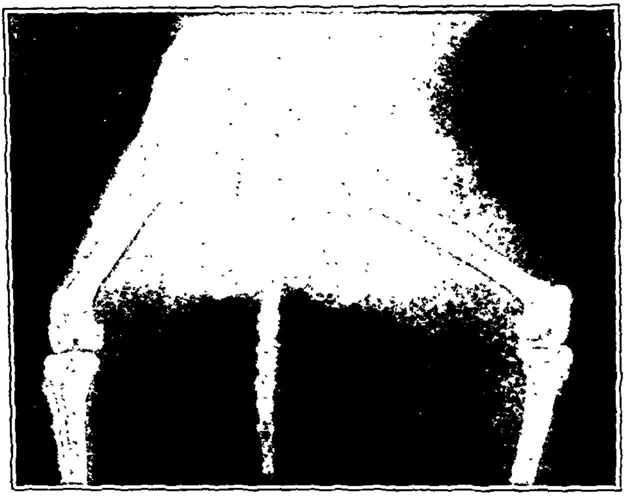

Fig. 2 (cat 216).—Roentgenogram of the posterior portion of the body of a live cat with a deafferented (one thousand, one hundred and fifty-eight days) and sympathectomized (seven hundred and sixty-three days) leg. There are subluxation of the hip and an increase in density of the head and the shaft of the femur on the left.

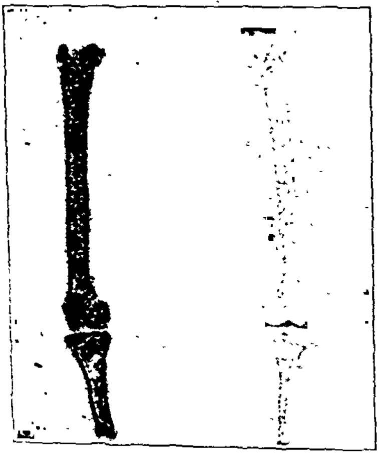

Fig. 3 (cat 216).—Roentgenogram of the cleaned bones of the hindlimbs. There is an increase in the diameter and density of the head of the femur on the right. This roentgenogram has been reversed in respect to figure 2.

The craniocaudal and dorsoventral diameters of the normal and the altered heads of the femurs are given in table 2. A notable difference between the measurements on the two sides was seen in all animals except cat 277, in which only slight gross changes were found in the denervated hip joint. This cat did not move about as much as the others, although all were free in the large outdoor cage previously mentioned. The femurs from cats which were considerably restricted in their movements showed no alterations roentgenographically five hundred and fifty days after deafferentation. These cats are under observation and have not yet been killed.

The gross appearance of the femurs and coxal bones from paired hindlimbs of the same animal only one of which was denervated is shown in figure 4. Those on the right present a picture similar to hypertrophic arthritis. The hyaline articular cartilages are completely worn off from considerable portions of the apposed upper surfaces, where marked bony polishing is present. Enlargement of the affected head and acetabular fossa, synovial fraying and noticeable thickening of the capsule about the acetabular margin also are evident.

TABLE 2.—*Dorsoventral and Craniocaudal Diameters of Heads of Femurs*

	Normal Side		Side Operated On	
Cat	Dorsoventral Diameters, Cm.	Craniocaudal Diameters, Cm.	Dorsoventral Diameters, Cm.	Craniocaudal Diameters, Cm.
216	1.10	1.10	1.40	1.25
276	1.09	1.05	1.12	1.10
236	1.02	1.00	1.10	1.09
288	1.15	1.18	1.22	1.22
238	1.08	1.05	1.10	1.10
277	1.23	1.23	1.24	1.23

The appearance of the articular cartilage and the underlying spongiosa of the head of the femur from the normally innervated limb is shown in frontal section in figure 5. The normal hyaline cartilage, the compacta and the wide medullary spaces in the spongiosa are shown clearly. A similar section taken near the capitular fossa from the head of the femur of cat 277, on which deafferentation was performed one thousand and eight days previously and sympathectomy seven hundred and thirty-four days previously, is shown under somewhat lower magnification in figure 6. Here the cartilage is thicker than that shown in figure 5, as the two sections are not from corresponding areas of the joint capsule. For some reason this animal did not move about much. No roentgenographic changes were found in the bones, and only the slightest sign of wear of the cartilage was grossly evident in the region represented. However, detritus and superficial erosion and degeneration, with deeper striation or so-called fibrillation, were present in the cartilage. There was no sclerosis of the spongiosa.

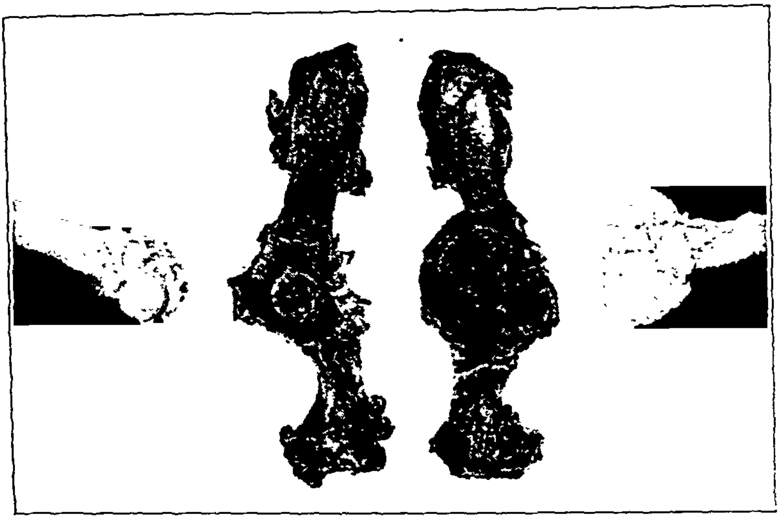

Fig. 4 (cat 216).—Paired femurs and coxal bones. The denervated coxal bone and head of the femur on the right show widening, erosion and bony polishing of both articular surfaces. Synovial tags are present on the inner surface of the thickened capsule; × 0.55.

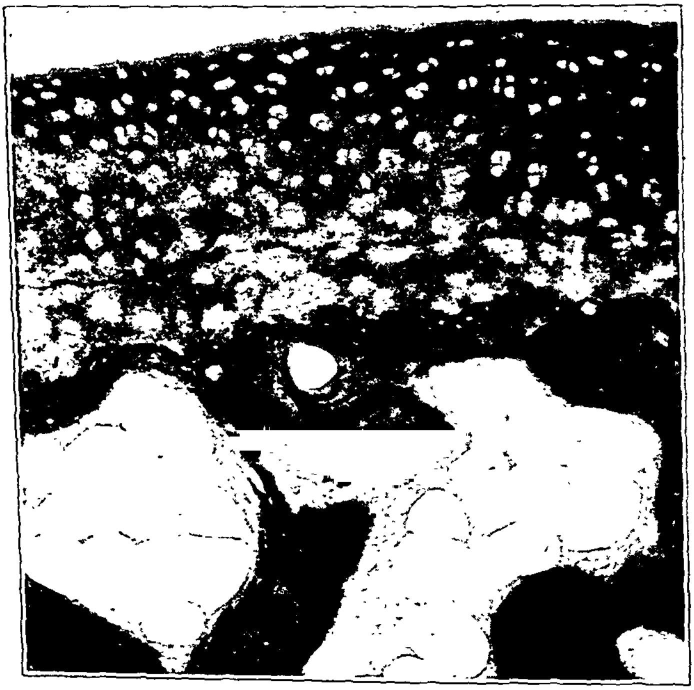

Fig. 5.—Photomicrograph of a frontal section of the articular surface of the head of the femur of a normally innervated limb; × 110. The cartilage and spongiosa are normal in appearance.

More pronounced changes are shown in figure 7, a section of the head of the femur from cat 288, on which deafferentation was done nine hundred and thirty-three days previously and sympathectomy seven hundred and thirty-two days previously. The calcified layer seems to be intact and cellular, although the underlying spongiosa shows evident signs of new bone formation by the presence of bony sclerosis or so-called eburnation. On comparing this figure with figure 5, it is evident that the medullary spaces are being reduced and that haversian systems are being formed in the spongiosa, producing a thickened compacta. This suggests that the eburnation probably is a functional response and does not require removal of the calcified cartilage from the underlying compacta and direct mechanical stimulation.

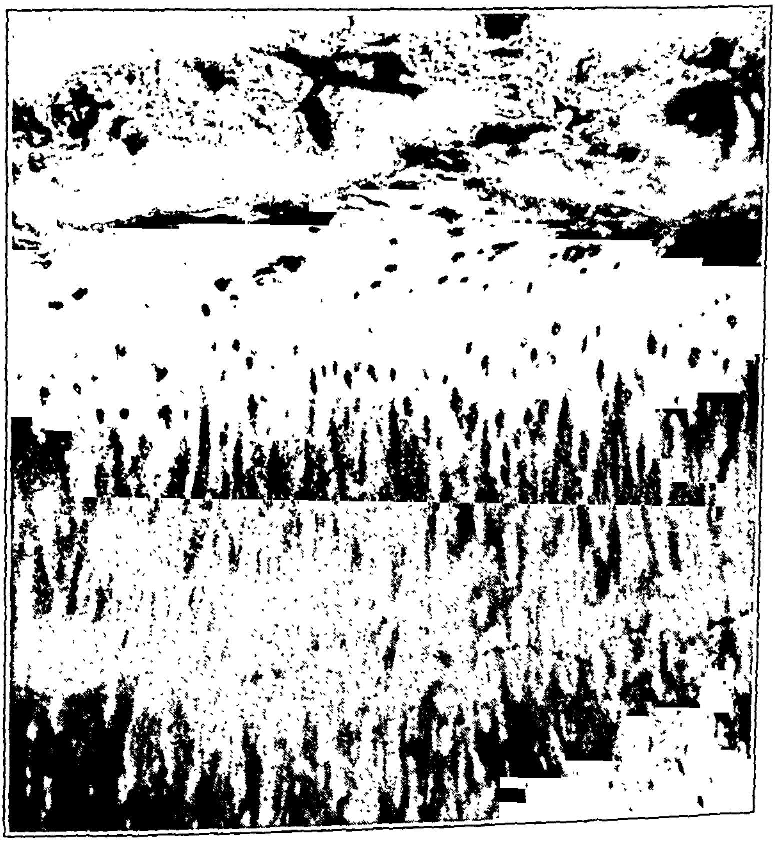

Fig. 6 (cat 277).—Photomicrograph of a frontal section of the articular surface near the capitular fossa of the head of the femur of a deafferented (one thousand and eight days) and sympathectomized (seven hundred and thirty-four days) hindlimb; × 100. There is superficial detritus with striation of the hyaline cartilage.

A still more pronounced stage of this condition is shown in figure 8, a photomicrograph of a section from the head of the femur from a denervated hindlimb of cat 236 under low power magnification. The cartilage is completely worn away from a large area of the head of the femur. A remnant of ligamentum teres, which was always destroyed in these cases of marked alterations in the joints, is seen at *l. t.* Bony sclerosis is present throughout the head but is most marked directly beneath the bare area. On the right of this figure one can see the extension of newly formed cartilage marginally and endochondral ossification extending into it. Deafferentation was done seven hundred and thirty-one days, and sympathectomy one thousand and ninety-seven days, previous to the death of the cat.

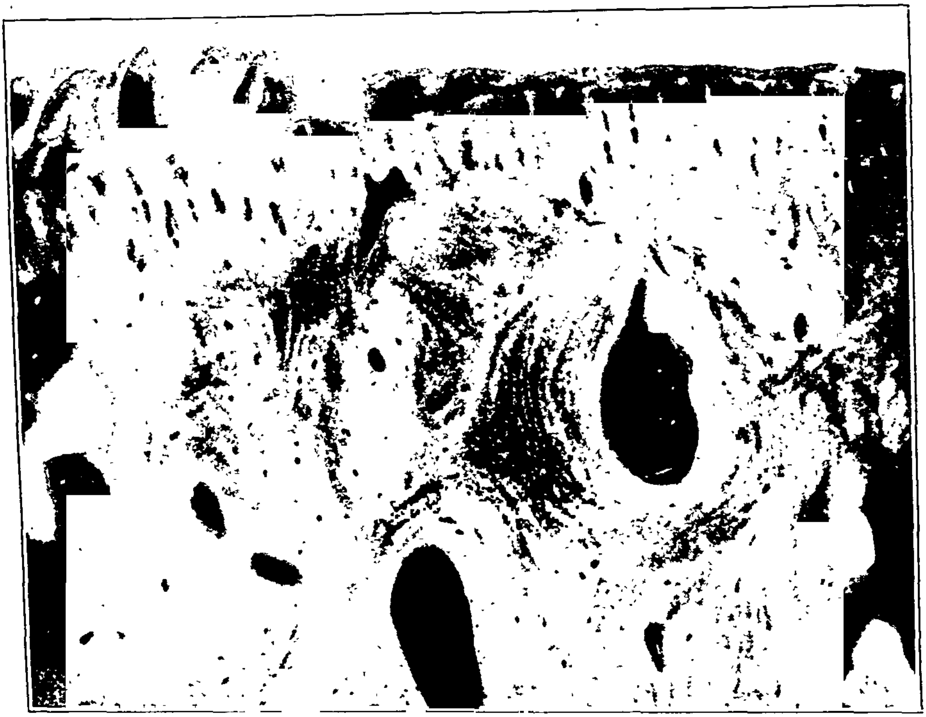

Fig. 7 (cat 288).—Photomicrograph of a frontal section of the head of the femur of a deafferented (nine hundred and thirty-three days) and the sympathectomized (seven hundred and thirty-two days) hindlimb; × 110. There are degeneration and destruction of the uncalcified hyaline cartilage and sclerosis of the spongiosa. The calcified cartilage is still intact.

A cross-section of the acetabulum from this animal, the head of the femur of which is shown in figure 8, is represented in figure 9 under low power magnification. There is pronounced marginal synovial fraying, and the hyaline articular cartilage on the left has been worn away for a distance of about 2 mm. All of the cartilage is destroyed, and the underlying spongiosa is eburnated. The right hand portion of

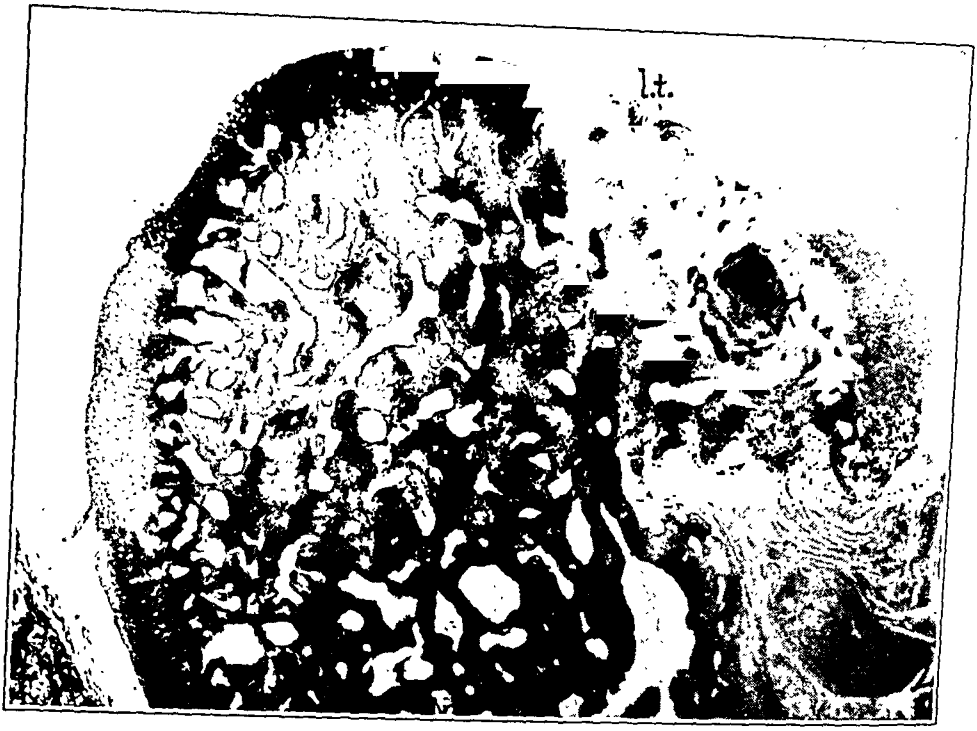

Fig. 8 (cat 236).—Photomicrograph of a frontal section from the head of the femur of a deafferented (seven hundred and thirty-one days) and sympathectomized (one thousand and ninety-seven days) hindlimb; × 12. The remnant of the ligamentum teres is indicated by *l.t.* The cartilage is completely worn away from a large area of the articular surface. There are bony sclerosis throughout the head and new cartilage formation on the right, with endochondral ossification extending into it.

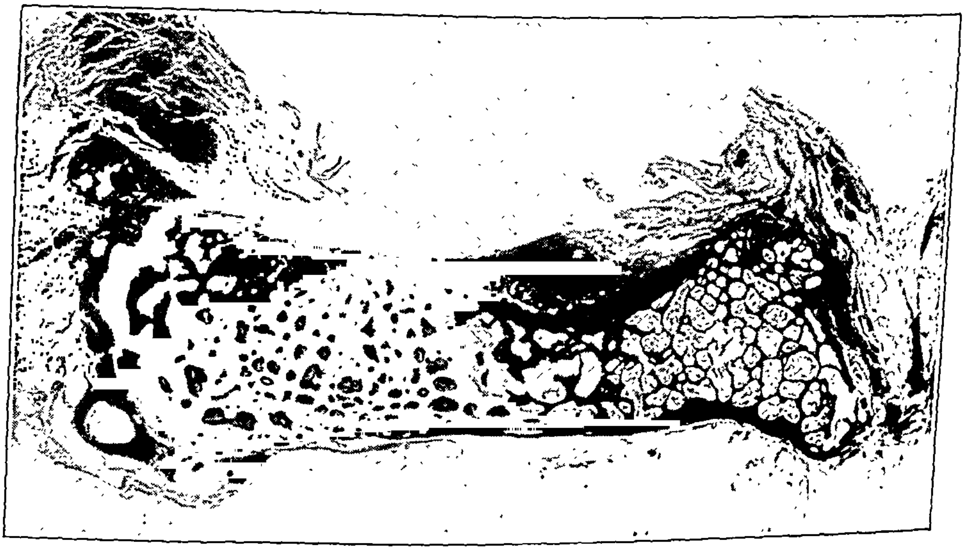

Fig. 9 (cat 236).—Photomicrograph of a cross-section of the acetabulum from the same deafferented limb shown in figure 8; × 5. The articular cartilage on the left is completely destroyed, and the surface of the joint is worn. There is sclerosis of the spongiosa on the left. The surface of the joint on the right is covered with new fibrocartilage in which endochondral ossification is taking place. There is no sclerosis in the spongiosa on the right, and synovial tagging and fraying are present.

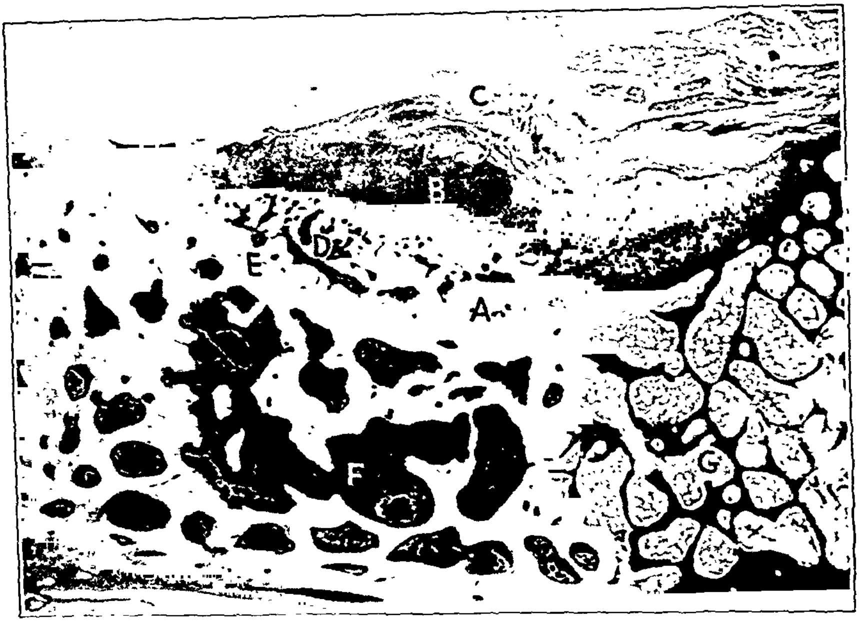

Fig. 10.—Photomicrograph of the same section shown in figure 9; × 12. *A* indicates hyaline cartilage of a former articular surface; *B,* new fibrocartilage continuous with the synovial membrane at *C; D,* a region in which endochondral ossification is taking place; *E,* a calcified cartilage zone; *F,* a large fibrous area in the medullary cavity, and *G,* normal-appearing medullary spaces and spongiosa.

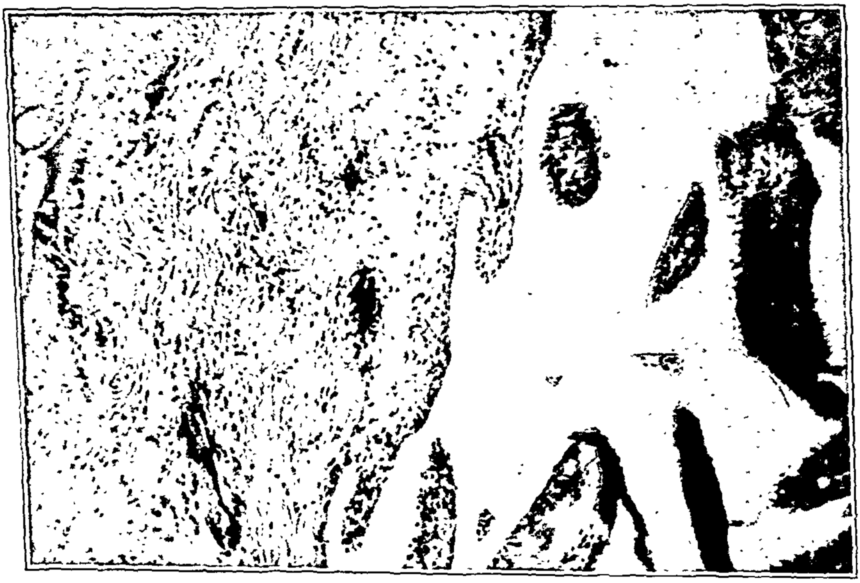

Fig. 11 (cat 216).—Photomicrograph of a section of the synovial membrane from the hip joint from a deafferented (one thousand, one hundred and fifty-eight days) and sympathectomized (seven hundred and sixty-three days) hindlimb. There are numerous synovial villi and no evidence of inflammation.

this acetabulum is shown under higher magnification in figure 10. The old joint surface at *A* is covered with fibrocartilage, *B*, directly continuous with the synovial membrane at *C*. At *D*, endochondral ossification has taken place, apparently in the proximity of vascular loops, which appear to have penetrated the calcified cartilage at *E*. A large fibrous area is seen in the marrow at *F*, but the spongiosa at *G* is normal and contrasts markedly with that on the left under the denuded surface.

A section of the synovial membrane from a similar hip joint is shown in figure 11. Numerous synovial tags are present, but there is no evidence of an inflammatory reaction in this or in the other joints showing these changes, and the blood vessels appear normal in distribution and size.

COMMENT

Bony sclerosis or eburnation has been thought to result from the presence of necrotic cartilage or bone (Axhausen[4]), from a hyperemic condition of the medullary spaces (Wollenberg[5]), from a sclerosing osteitis (Knaggs[10]) or in compensation to "cartilage erosion" (Allison and Ghormley[11]). The fact that the bones from the denervated legs without marked alterations in the hip joints show no other changes suggests that the increase in weight in the femurs and tibias of the denervated limbs is a functional response to the altered conditions in the hip joints. This increase in weight may be a compensatory reaction to the destruction of the cartilage on the head of the femur, or it and the arthritic changes may have resulted from the use of the limb in an abnormal position. This supposition is supported by the occurrence of changes in the hip joints only in the deafferented limbs of animals which had considerable freedom.

Wright and Pemberton[12] found that 75 per cent of arthritic subjects have a lower peripheral surface temperature than normal persons under comparable circumstances. Hinsey[13] found a marked lowering of skin temperature in the deafferented limbs of cats. Just why section of the posterior roots should cause such a fall in skin temperature is not known, but several possibilities suggest themselves. If the dorsal roots contain vasodilator fibers, these would be interrupted, and their loss would probably result in a decreased peripheral skin temperature

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[10] Knaggs, R. L.: The Inflammatory and Toxic Diseases of Bone, Bristol, John Wright & Sons, Ltd., 1926.

[11] Allison, N., and Ghormley, R. K.: Diagnosis in Joint Disease, New York, William Wood & Company, 1931.

[12] Wright, L., and Pemberton, R.: The Peripheral Surface Temperature in Arthritis, Arch. Int. Med. **45:**147 (Jan.) 1930.

[13] Hinsey, J. C.: Observations on Skin Temperatures in Hind Limbs Deprived of Their Sensory and Sympathetic Nerve Supply, Am. J. Physiol. **109:** 53, 1934.

Another possibility is that the afferent fibers from the skin exert an inhibiting effect on the preganglionic vasoconstrictor sympathetic fibers and that interruption of the sensory pathway leads to an overactivity of the vasoconstrictor fibers. It is possible that the reduced peripheral skin temperature found in arthritic patients is the result of a decreased sensory supply to the limbs. Pearson[14] and Newman and Corbin[14a] reported a striking decrease in vibratory sensibility of the lower extremities in persons after the fifth decade of life. Hypertrophic arthritis is known to be a disease seen most commonly in the later decades of life. Whether a patient with this condition has a more reduced peripheral sensibility than an unaffected person of the same age, I am not ready to assert, but work in progress suggests that this may be the case (Newman and Corbin).

A statement from the report of the Second Conference on Rheumatic Diseases of the Mayo Clinic (Hench[15]) is likewise somewhat suggestive in this respect, for it is there stated: "No explanation was given as to why many badly worn joints, with extensive hypertrophic arthritis, are painless, whereas other joints only slightly altered are so painful that locomotion is difficult. Only about 7 per cent of Keefer's patients suffered pains in the joints." Eloesser[9] also stressed the importance of anesthesia and consequent trauma in the development of Charcot-like joints in the deafferented limbs of cats.

Ellis[16] found a steady decrease in the number of Purkinje cells in man with advancing age, and Inukai[17] made the same observation in rats. Duncan[18] found a 10 per cent decrease in the number of ventral root fibers in old rats. He also found a small number of fibers exhibiting wallerian degeneration in the peripheral nerves of animals of all ages. This would tend to show that a continual slight degeneration of nerve fibers occurs throughout life. Recently Corbin and Gardner[19] have found a diminution in the number of spinal root myelinated fibers in the senile human subject.

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[14] Pearson, G. J.: Effect of Age on Vibratory Sensibility, Arch. Neurol. & Psychiat. **20**:482 (Sept.) 1928.

[14a] Newman, H. W., and Corbin, K. B.: Quantitative Determination of Vibratory Sensibility, Proc. Soc. Exper. Biol. & Med. **35**:273 (Nov.) 1937.

[15] Hench, P. S.: Report on Second Conference on Rheumatic Diseases, Proc. Staff Meet., Mayo Clin. **8**:573 (Sept. 20) 1933.

[16] Ellis, R.: Norms for Some Structural Changes in the Human Cerebellum from Birth to Old Age, J. Comp. Neurol. **32**:1, 1920.

[17] Inukai, T.: On the Loss of Purkinje Cells, with Advancing Age, from the Cerebellar Cortex of the Albino Rat, J. Comp. Neurol. **45**:1, 1928.

[18] Duncan, D.: A Determination of the Number of Nerve Fibers in the Eighth Thoracic and the Largest Lumbar Ventral Roots of the Albino Rat, J. Comp. Neurol. **59**:47, 1934.

[19] Corbin, K. B., and Gardner, E. D.: Decrease in Number of Myelinated Fibers in Human Spinal Roots with Age, Anat. Rec. **68**:63 (April 25) 1937.

Eloesser's work showed that deafferentation alone, without concomitant sympathectomy, suffices to produce Charcot-like joints. Tabetic arthropathy *is a clinical condition in which the only known* causative local factor is anesthesia, but how diminished sensibility of a joint can produce a "deforming arthritis" is not known. A number of ancillary factors, such as senility and arteriosclerosis, undoubtedly contribute to its pathogenesis in man, but with diminished sensibility, the proprioceptive mechanism, which ordinarily protects against malposition and motion beyond the normal range, is impaired, so that areas of the articular surfaces, ligaments and capsules, unadapted for the stresses to which they are subjected, may be traumatized. If there also is a diminished blood supply as the result of senile arteriosclerosis and of the vasoconstriction, which may accompany reduced sensibility, the hyaline articular cartilage may suffer nutritional disturbances and become more susceptible to traumatic injuries. As soon as destruction *of the cartilage has begun, the initial wear is intensified* through the increased friction between less resistant and roughened surfaces. These, to be sure, are merely suggestions, and I realize that the question will have to be studied from many other aspects before a definite decision can be reached.

Dr. J. C. Hinsey furnished the material for this study.

MALIGNANT TUMORS OF MECKEL'S DIVERTICULUM

REPORT OF A CASE OF LEIOMYOSARCOMA

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ROCHESTER, MINN.

A malignant tumor of Meckel's diverticulum is rare enough to be considered a pathologic curiosity. The literature on other lesions associated with Meckel's diverticulum, however, is increasing each year. We have therefore thought it opportune to combine the report of a case of a malignant tumor of Meckel's diverticulum with a general survey of the literature.

Meckel's diverticulum is a developmental anomaly of the intestinal tract which is found in about 2 per cent of all adults. The mechanism responsible for the production of this anomaly, as is well known, is failure of the omphalomesenteric duct and its accompanying vessels to become completely obliterated. Normally this obliteration takes place in the third to the fifth week of embryonic life. The yolk stalk may fail to become completely obliterated, leading in rare cases to an intestinal fistula opening through the umbilicus; occasionally the duct becomes obliterated, except at its distal part. In the latter instance an umbilical fistula is formed with secretion from still active glandular elements in the mucosa of the open duct. Occasionally these cells may undergo hyperplastic changes and form a neoplasm of the umbilicus. In other instances the proximal and distal parts of the omphalomesenteric duct may be closed, but an opening may remain in the middle part of the duct. As a result of the secreting activity of the remaining cells of the duct, a retention cyst may be formed, a so-called enterocystoma. In case only the proximal part of the omphalomesenteric duct is closed, a true Meckel's diverticulum is formed. It appears, however, that any of these various types of developmental anomalies may be combined (fig. 1).

True Meckel's diverticulum is usually located in the ileum about 100 cm. from the ileocecal valve; in rare cases, however, it may be found anywhere in the gastro-intestinal tract from the cardia to the rectum. Such diverticula vary greatly in size, but they usually reach from 2.5 to 10 cm. in length and are most frequently found on the antimesenteric border. With these variations in mind, it will be readily understood that the location and the gross appearance may not be sufficient evidence on which to base a diagnosis of true Meckel's diverticulum. Attempts have been made by microscopic examination to lay down definite requirements for the diagnosis of such a diverticulum.

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† From the Division of Surgery, the Mayo Clinic.

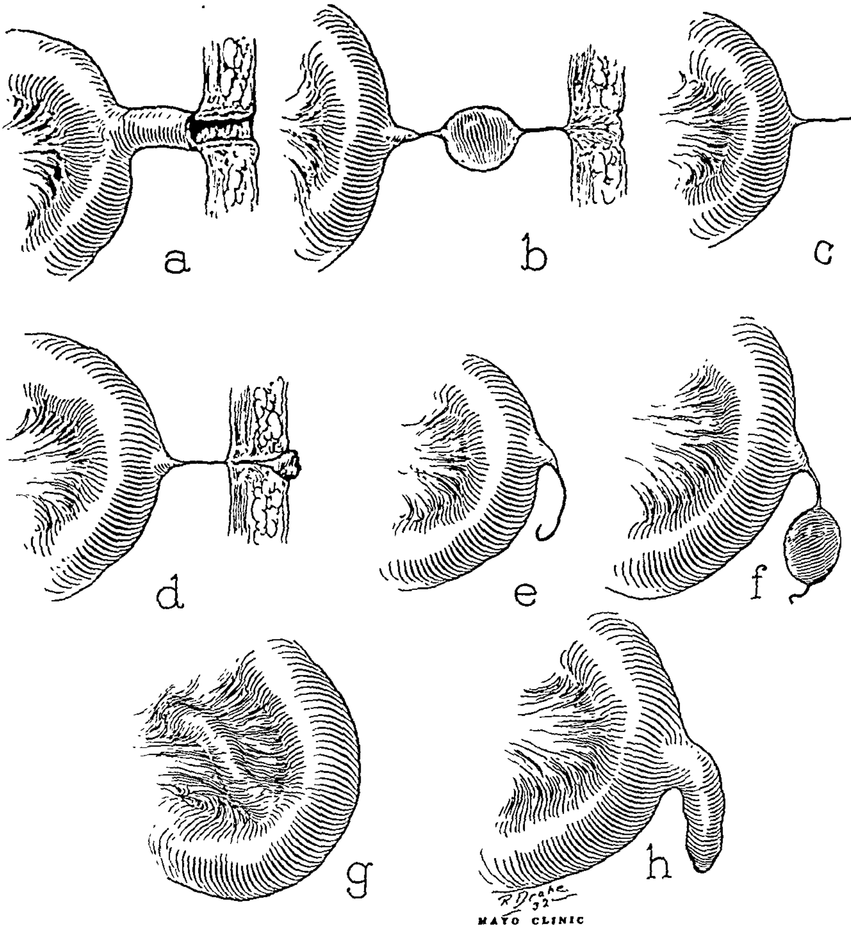

Fig. 1.—Various types of developmental anomalies: *a,* patent duct opening onto the abdominal wall at the umbilicus; *b,* the duct occluded at its end so that a cyst is formed somewhere in its length; *c,* the duct obliterated but remaining attached to the umbilicus; *d,* the duct remaining attached to the umbilicus and with intestinal mucosa at its outer end; *e,* the duct obliterated and hanging with a free end within the abdominal cavity; *f,* the duct hanging within the abdominal cavity and forming a cyst; *g,* the duct lying within the mesentery of the small intestine, and *h,* the duct remaining as a small patent projection from the ileum. (This illustration was redrawn from Dixon and Steward.[4a])

These attempts, however, have proved only partly successful because of the somewhat inconsistent histologic characteristics of the mucosa of the diverticulum.

Farr and Penke,[1] in a review of the surgical files of the New York Hospital, found gastric mucosa reported in 6 of 13 Meckel's diverticula. According to Schaetz,[2] 57 per cent of 30 Meckel's diverticula that were examined carefully contained only normal ileac mucosa. In the remaining 13 diverticula in his series, jejunal mucosa was found in 3, gastric mucosa in 5, pancreatic tissue in 3, carcinoid tissue in 1 and peritoneal epithelium in 1.

As has been said, Meckel's diverticulum is only a developmental anomaly, and no doubt many people have gone through life without ever having had any symptoms from it. Studies of the records of 2,050 necropsies at the New York Hospital from 1916 to 1931 revealed Meckel's diverticulum as an incidental finding in 13 cases; it had given rise to intestinal strangulation in only 1 instance.

Meckel's diverticulum appears to be found more frequently in males than in females, the incidence according to Christie[3] being 75 per cent in males as compared to 25 per cent in females, with an incidence of approximately 1.1 per cent in all persons.

It appears from the increased number of reports on the subject in last year's medical literature that Meckel's diverticulum is potentially the source of many different pathologic conditions, diverticula having been reported to have given rise to pathologic changes in from 25 to 33 per cent of cases. The pathologic changes associated with Meckel's diverticulum are given in the following outline. No doubt with greater experience this outline will prove to be incomplete. It is presented here in the hope that it may facilitate a survey of the various pathologic potentialities of Meckel's diverticulum.

Pathologic Conditions Associated with Meckel's Diverticulum

A. Mechanical disturbances:

1. Gangrene of the diverticulum after strangulation or excessive rotation of a long diverticulum
2. Intestinal ileus following eversion of part of the intestine into the diverticulum or invagination of the diverticulum into the intestines, strangulation of the intestine by the diverticulum or its band formations or kink formations by pulling of bands and adhesions.
3. Disturbances caused by a hernial sac containing a diverticulum
4. Disturbances arising when a diverticulum is associated with the developmental anomaly of congenital ileac atresia and ileac stenosis

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[1] Farr, C. E., and Penke, Madeline: Meckel's Diverticulum, Ann. Surg. **101**:1026-1041 (April) 1935.

[2] Schaetz, Georg: Beiträge zur Morphologie des Meckel'schen Divertikels (Ortsfremde Epithelformationen im Meckel), Beitr. z. path. Anat. u. z. allg. Path. **74**:115-224, 1925.

[3] Christie, A. U., cited by Michael and Bell.[14]

- B. Inflammatory disturbances, varying from mild catarrhal inflammation to gangrene, with perforation and peritonitis (diverticulitis):
  - 1. Nonspecific inflammation, caused by:
    - (*a*) Trauma
    - (*b*) Foreign bodies (calculi)
    - (*c*) Parasites
    - (*d*) Idiopathic diverticulitis
  - 2. Specific inflammation, caused by:
    - (*a*) Tuberculosis
    - (*b*) Typhoid
- C. Heterotopic tissue formations:
  - 1. Accessory pancreatic tissue
  - 2. Normal, hypertrophic or ulcerating mucosa from the gastro-intestinal tract, leading to diverticulitis, with or without ulceration and subsequent intestinal hemorrhage
- D. Neoplastic disease (exclusive of enterocystoma):
  - 1. Benign tumor:
    - (*a*) Myoma
    - (*b*) Lipoma
    - (*c*) Carcinoid tumor
    - (*d*) Neuroma
    - (*e*) Papilloma
  - 2. Malignant tumor:
    - (*a*) Carcinoma
    - (*b*) Sarcoma

So-called heterotopic tissue formations in Meckel's diverticulum have for many years attracted the interest of embryologists, histologists and pathologists. Most frequently such tissue consists of aberrant pancreatic tissue, gastric mucosa or mucosa from other portions of the intestinal tract. These various tissue formations may be present alone, or they may be mixed, and they may or may not appear grossly as a tumor. A most extensive and interesting investigation of heterotopic tissue formations was made by Schaetz. The clinical importance of these particular anomalies is emphasized by the occasional finding of ulcerations and subsequent hemorrhage in heterotopic tissues.[4]

In connection with benign tumors of Meckel's diverticulum it may be mentioned that a myoma giving rise to ileus was removed from a

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[4] (*a*) Dixon, C. F., and Steward, J. A.: Diverticulum with Hemorrhage: Omphaloadenoma, S. Clin. North America **12:**1025-1031 (Aug.) 1932. (*b*) Schullinger, R. N., and Stout, A. P.: Meckel's Diverticulum: Report of a Case of Hemorrhage in the Bowel Associated with a Meckel's Diverticulum that Presented an Adenoma Composed of Gastric and Duodenal Glands, Arch. Surg. **28:** 440-466 (March) 1934.

9 year old boy by Höpfner.[5] A lipoma in the same location was described by Macé de Lépignay.[6] Of greater importance than these, however, are the so-called carcinoid tumors.

Oberndorfer[7] in 1907 reviewed a few cases of tumor of the small intestine in which the growths had the same microscopic picture as carcinoma but differed in several other respects, enough so to warrant separation of this type of tumor from the malignant tumors and classification of it under the "carcinoid tumors." Lubarsch[8] and others had earlier called attention to this group of tumors. In the same paper Oberndorfer described finding a carcinoid tumor of Meckel's diverticulum in a man 68 years of age who had died of cerebral arteriosclerosis. Later, similar reports appeared in the literature. Schaetz in 1925, in a study of 30 cases of Meckel's diverticulum, found small groups of epithelial cells in the tip of the diverticulum in a 69 year old man who had died of bronchopneumonia. These cells had the characteristics of those found in carcinoid tumor. Stewart and Taylor[9] reported finding a typical carcinoid tumor the size of a pea in a diverticulum removed at postmortem examination from a man 54 years old who had died of coronary sclerosis. Finally, Price[10] in 1935 removed an inflamed and obstructed Meckel's diverticulum from a woman 54 years of age who had had generalized abdominal pain and signs of peritonitis for one day. On microscopic examination the diverticulum was found to contain a carcinoid tumor.

Hicks and Kadinsky[11] reported a case of carcinoid tumor in 1922, but Stewart and Taylor, who had occasion to examine the slides, were of the opinion that the lesion was not a carcinoid tumor but heterotopia of the gastric mucosa.

CARCINOMA OF MECKEL'S DIVERTICULUM

The following are abstracts of cases of carcinoma of Meckel's diverticulum reported in the literature.

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[5] Höpfner, E.: Ein eigenartiger Fall von Divertikel-Ileus, Arch. f. klin. Chir. **97**:1058-1073 (April 4) 1912.

[6] de Lépignay, Macé, cited by Hässner.[23]

[7] Oberndorfer, Siegfried: Karzinoide Tumoren des Dünndarms, Frankfurt. Ztschr. f. Path. **1**:426-432, 1907.

[8] Lubarsch, cited by Franke.[15]

[9] Stewart, M. J., and Taylor, A. L.: Carcinoid Tumour of Meckel's Diverticulum, J. Path. & Bact. **29**:135-136, 1926.

[10] Price, I.: Carcinoid Tumour of a Meckel's Diverticulum: Report of a Case, Brit. J. Surg. **23**:30-34 (July) 1935.

[11] Hicks, J. A. B., and Kadinsky, S.: A Case of "Carcinoid Tumour" of Meckel's Diverticulum, Lancet **2**:70 (July 8) 1922.

Wiseley[12] in 1931 reported intestinal resection for medullary carcinoma of Meckel's diverticulum located about 76 cm. from the ileocecal valve in a man 41 years of age.

In the laboratory of surgical pathology at the Johns Hopkins Hospital, 11 instances of Meckel's diverticulum were encountered among 50,000 pathologic specimens. According to Copeland,[13] 1 of these diverticula was the seat of an adenocarcinoma involving the umbilicus, and it had grown to such an extent that the exact relations of the ileum, the diverticulum and the umbilicus were rather indistinct.

Michael and Bell[14] in 1932 described an adenocarcinoma of Meckel's diverticulum removed at operation from a man 76 years of age.

Franke[15] in 1933 described a necrotic adenocarcinoma of Meckel's diverticulum removed at operation from a 54 year old man.

Rexwald Brown[16] in 1933 described a degenerating medullary carcinoma, probably of Meckel's diverticulum, removed at operation from a man 62 years of age. The tumor was about the size and shape of a cauliflower and had given rise to general peritonitis.

Gray and Kernohan[17] reported an intestinal resection of part of the ileum for tumor of a diverticulum that had doubly invaginated the ileum. The patient was a woman 37 years of age. The tumor was the size of a walnut and was made up of two well differentiated parts, the proximal part consisting of heterotopic gastric mucosa and the distal part of adenocarcinomatous tissue of grade 2. The main clinical symptom was vague abdominal distress. Bimanual palpation revealed a slightly tender mass in the ileocecal region, but the peculiar thing about this palpatory finding was that one day the tumor could be easily felt, whereas on other days it was difficult or even impossible to feel it at all.

SARCOMA OF MECKEL'S DIVERTICULUM

While sarcoma of the small intestine is comparatively rare, it appears that a slightly greater number of sarcomas of the small intestine have been reported than of carcinomas in that region. In 569 cases of carcinoma Lubarsch[8] found only 0.3 per cent of carcinomas of the ileum. Magnusson[18] collected reports of 98 cases of sarcoma of the small intestine from the literature in 1934. In this series there appeared to be an equal incidence of sarcoma of the ileum and sarcoma of the jejunum, a preponderance of males being affected. In the 91 cases in which the sex was stated, 61 of the patients were males and 30 were females, their ages varying from 5 days to 81 years. Magnusson did not state, however, how many cases of sarcoma of Meckel's diverticulum were included in this series.

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[12] Wiseley, A. N.: Medullary Carcinoma of Meckel's Diverticulum, J. A. M. A. **96**:1949-1950 (June 6) 1931.

[13] Copeland, cited by Wiseley.[12]

[14] Michael, Paul, and Bell, H. G.: Primary Adenocarcinoma Arising in a Meckel's Diverticulum, Surg., Gynec. & Obst. **54**:95-97 (Jan.) 1932.

[15] Franke, Kurt: Ueber ein primäres Carcinom in einem Meckelschen Divertikel, Ztschr. f. Krebsforsch. **39**:206-216 (April) 1933.

[16] Brown, Rexwald: Carcinoma of Meckel's Diverticulum, S. Clin. North America **13**:1283 (Dec.) 1933.

[17] Gray, H. K., and Kernohan, J. W.: Unpublished data.

In a review of the literature we have been able to find reports of 12 cases of sarcoma of Meckel's diverticulum. In addition to this, there are 2 unpublished cases from the Mayo Clinic. It appears, therefore, that sarcomas of Meckel's diverticulum do not account for more than from 12 to 14 per cent of all sarcomas of the small intestine. The following are abstracts of cases of sarcoma of Meckel's diverticulum which were reported:

The first report of a case of sarcoma of Meckel's diverticulum was made by Virchow, who, according to Fried,[19] described the tumor in a new-born infant. It was a spindle cell sarcoma that pressed out through the umbilical ring. The sex of the infant was not given.

Kaufmann[20] in 1890 described a case of myxosarcoma telangiectodes.

Fried[19] in 1902 described a myosarcomatous tumor the size of two fists which was found at postmortem examination on a man 55 years of age. The tumor was located about 120 cm. above the ileocecal valve, and there was metastasis to the regional lymph nodes and to the liver. The clinical diagnosis in this case was acute peritonitis (intestinal embolus).

The Basler[21] collection contains the report of a case in which a spindle cell sarcoma of Meckel's diverticulum the size of a hen's egg was found in a woman 72 years of age.

Tschiknawerow[22] found a spindle cell sarcoma of Meckel's diverticulum during postmortem examination on a woman 62 years of age, who had died from fibrinopurulent acute peritonitis following torsion of the ileum, with necrosis and perforation of the diverticulum.

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[18] Magnusson, Ragnar: Sarcoma of Small Intestine, in Connection with a Case of Haemangiosarcoma of the Jejunum, Acta chir. Scandinav. **73**:576-590, 1934.

[19] Fried, cited by Franke.[15]

[20] Kaufmann, cited by Franke.[15]

[21] Basler, cited by Kaufmann, Eduard: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, Berlin, W. de Gruyter & Co., 1922, vol. 1, p. 571.

[22] Tschiknawerow, Leon: Zur Kenntnis der pathologischen Gewebsbildungen im Meckel'schen Divertikel, Berl. klin. Wchnschr. **48**:1676-1679 (Sept. 11) 1911.

Hässner[23] found at necropsy a degenerating sarcoma of Meckel's diverticulum in a man 50 years of age who had been operated on after a few days' illness for beginning peritonitis. He had died two days after the operation.

Symmers[24] reported finding a leiomyosarcoma of Meckel's diverticulum in a man aged 22. The lesion was discovered incidentally during an operation for hernia and was situated 30 cm. above the ileocecal valve. No clinical symptoms were associated with it.

Black[25] reported removal of a huge tumor weighing 2,460 Gm. from a woman 59 years of age. The tumor was a papillomatous cystadenoma of potentially malignant type and was thought to have originated in a diverticulum (either acquired or congenital) in the sigmoid colon.

Crile and Portmann[26] reported a case in which a spindle cell sarcoma of Meckel's diverticulum was removed from a woman 41 years of age; the tumor was the size of a pear. At the time of the physical examination a small mass was palpated in the right lower abdominal quadrant.

Mathews[27] in 1925 removed a myoma from the ileum of a man 44 years of age. The patient was referred to him because of a large abdominal mass reaching from the culdesac to about the level of the umbilicus. During examination the tumor had suddenly lost its tenseness simultaneously with the onset of severe abdominal pain, for which reason emergency laparotomy was performed after a lapse of two hours. The patient recovered and felt fine for about four and a half years, when the hypogastric tumor recurred. It was removed after a few months. At the second examination there were palpatory signs of recurrence. The tumor removed at the second operation was a leiomyosarcoma, a finding which makes it reasonable to assume that the tumor may have had sarcomatous characteristics at the time of the first operation.

According to Oberndorfer, there are all stages of transition from myoma to myosarcoma, a peculiarity which is the basis of one of the greatest controversies regarding tumors of the intestinal tract.

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[23] Hässner, Hugo: Zur Pathologie des Meckelschen Divertikels (Fall von Sarkom des Meckelschen Divertikels), Frankfurt. Ztschr. f. Path. **14**:501-516, 1913.

[24] Symmers, Douglas: The Association of Malignant Myomata with Meckel's Diverticulum, Ann. Surg. **70**:183-187 (Aug.) 1919.

[25] Black, W. T.: Congenital Diverticula of the Intestines: Report of a Case of a Tumor Growing from the Tip of an Apparently Congenital Diverticulum in the Lower Sigmoid Region, Surg., Gynec. & Obst. **28**:473-477 (May) 1919.

[26] Crile, G. W., and Portmann, U. V.: A Primary Spindle Cell Sarcoma of Meckel's Diverticulum, Surg., Gynec. & Obst. **41**:615-617 (Nov.) 1925.

[27] Mathews, F. S.: Meckel's Diverticulum: A Report of Twelve Cases, Including One Tumor, Arch. Surg. **10**:720-729 (March) 1925.

König[28] in 1930 demonstrated a spindle cell sarcoma the size of a fist in a diverticulum. It led to fatal peritonitis due to necrosis of the tumor and perforation into the abdominal cavity.

Faust and Walters[29] in 1931 reported the removal of a diverticulum containing a fibrosarcoma from a man 62 years of age. The outstanding symptom in this case was intestinal hemorrhage leading to secondary anemia. The patient reentered the clinic in February 1936, that is, a little less than six years after removal of the intestinal tumor. Six months previously he had accidentally discovered a mass in the right lower abdominal quadrant, and this had gradually increased in size, causing distention and constipation of increasing severity. No recurrence of the gastro-intestinal hemorrhage was noted at the time of the second examination. There was moderate secondary anemia, the value for hemoglobin amounting to 9.7 Gm. per hundred cubic centimeters and the erythrocytes numbering 4,500,000 per cubic milli-

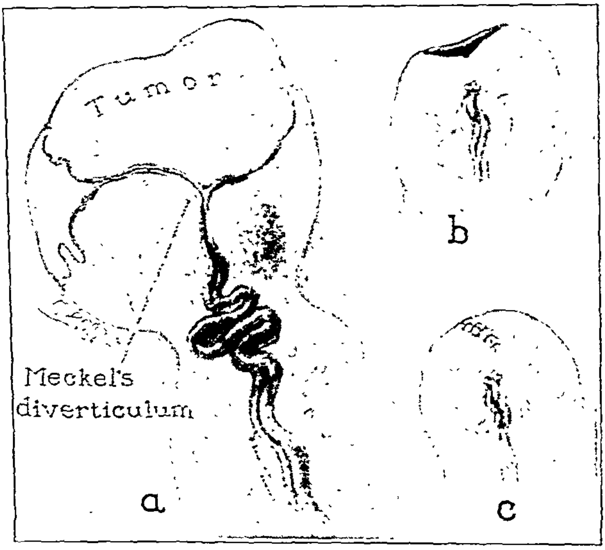

Fig. 2.—Part of the ileum with Meckel's diverticulum, shown in *a*. The blood vessels from the mesentery extend up to the tumor. In *b*, the blood vessels have been ligated and the diverticulum and the tumor excised, and in *c*, the opening in the ileum has been transversely sutured.

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28. König, E.: Sitzungsberichte aus chirurgischen Gesellschaften: XXXIX. Tagung der Vereinigung nordwestdeutscher Chirurgen am Freitag, dem 13. und Sonnabend, dem 14. Dezember 1929 im Allgemeinen Krankenhause Barmbeck in Hamburg. (Offizieller Bericht), Zentralbl. f. Chir. **57:**1107 (May 3) 1930.

29. Faust, L. S., and Walters, Waltman: Fibrosarcoma of a Meckel's Diverticulum Producing Intestinal Hemorrhage, Minnesota Med. **14:**233-236 (March) 1931.

meter of blood. A large mass was found that filled most of the right side of the abdomen and extended into the right flank. The most probable diagnosis was recurrence of the fibrosarcoma of the small intestine. Because of the size of the tumor and the poor general condition of the patient, exploratory laparotomy was not deemed advisable, and roentgen therapy was employed.

Kernohan,[30] in reviewing the records of approximately 140 cases in which a diverticulum was removed at operation or at necropsy at the Mayo Clinic, found 1 in which a leiomyosarcoma of Meckel's diverticulum had been removed from a 66 year old woman by Dr. Judd in 1926.[31] At operation 1 inch (2.5 cm.) of the ileum was excised, and a calcareous Meckel's diverticulum lying behind the uterus was removed. The diverticulum contained a tumor the size of a grapefruit, which on microscopic examination proved to be a myosarcoma, grade 2, with a neuroma.

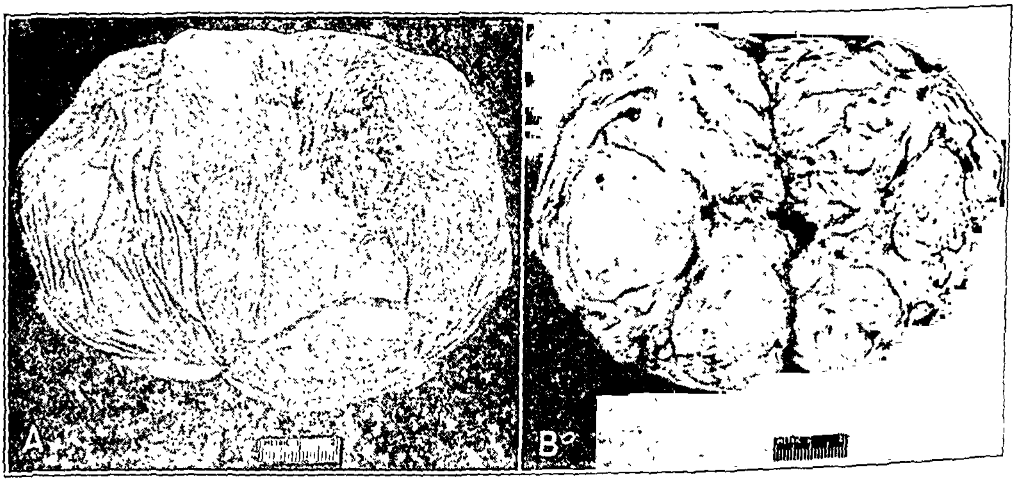

Fig. 3.—*A*, the diverticulum and tumor removed at operation. *B*, the specimen of the diverticulum and tumor cut open.

REPORT OF A CASE OF LEIOMYOSARCOMA OF MECKEL'S DIVERTICULUM

A man aged 62 registered at the clinic in January 1936. In the previous seven years he had been bothered with episodes of epigastric fullness followed by nausea, which were relieved by induced vomiting; these attacks were never associated with any real pain. On examination the patient did not appear to be sick. Palpation of the abdomen did not reveal any distention or tenderness or any masses. Bimanual rectal palpation, however, revealed a tumor in the culdesac anterior to the rectum; it measured about 5 by 7 cm., was movable and rather hard and had a smooth surface. It was not tender to pressure and appeared to be distinctly separate from the prostate gland and seminal vesicles. The palpatory findings, however, seemed to change from day to day. Proctoscopic examination proved the tumor to be extrinsic to the rectum and the lower part of the sigmoid colon. An enema of barium sulfate indicated a normal colon and terminal portion of the ileum. Examination otherwise gave negative results, except for the finding of a small duodenal ulcer on roentgenographic examination of the stomach. Abdominal exploration, performed on January 14, revealed an encapsulated tumor of the ileum, about 10 cm. in diameter, completely filling a diverticulum. One large vein 5 mm. in diameter and an artery half that size extended up from the mesentery of the ileum in a tortuous fashion over the side wall of the ileum and up into the tumor (fig. 2). These vessels were divided and ligated, after which the tumor was excised from the ileum with a cutting cautery: the opening in the ileum was closed transversely.

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[30] Kernohan, J. W.: Personal communication to the authors.

[31] This case will be reported subsequently.

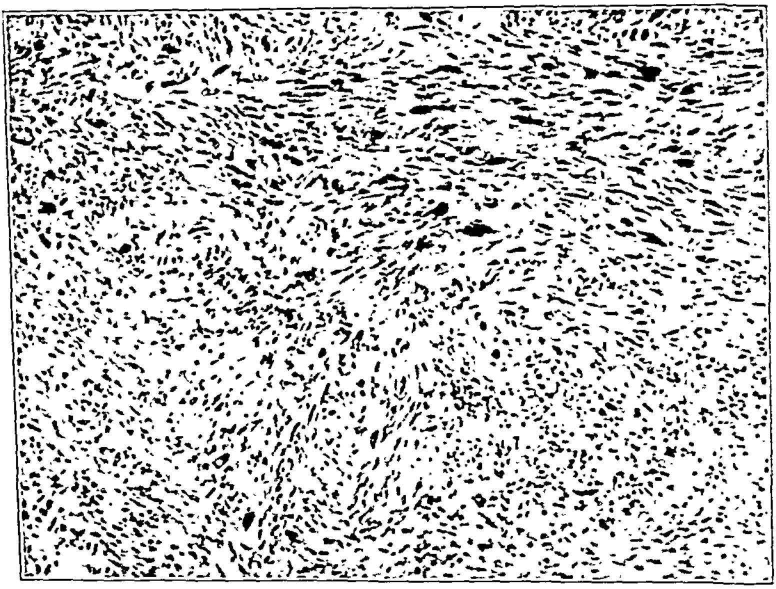

Fig. 4.—Section of the tumor, showing well differentiated bundles of smooth muscle tissue in a fibrous stroma. In some places the tumor cells are more clearly packed and more ovoid and hyperchromatic, an occasional mitotic figure being present. The diagnosis was leiomyosarcoma of a low grade of malignancy.

The postoperative course was uneventful. The tumor was pedunculated and ovoid and was firm and rubbery in consistency (fig. 3). It was situated in the submucosa on intramuscular layers of intestinal wall and was well encapsulated without producing any ulceration of the mucosa. Grossly, the tumor appeared to be composed of large whorls of myomatous tissue similar to that of leiomyoma of the uterus. Microscopically, it was found to be composed of well differentiated bundles of smooth muscle in tumor formation lying in a fibrous stroma. In some areas the tumor cells were more closely packed and more ovoid and hyperchromatic, and there was an occasional mitotic figure. The pathologic diagnosis was leiomyosarcoma of a low grade of malignancy (fig. 4).

COMMENT

In the survey that we have made we have found a total of 20 cases of malignant tumors of Meckel's diverticulum: 6 cases of carcinoma and 14 of sarcoma. In the 16 cases in which the sex was stated, 8 of the patients were males and 8 were females. In view of the statement that Meckel's diverticulum is found three times more frequently in males than in females, it would appear from this compilation that there may be a greater tendency toward a malignant growth in Meckel's diverticulum in females than in males. However, this finding may be entirely changed by analysis of a larger series of cases.

One of the cases of carcinoma reviewed in this series (the one reported by Gray and Kernohan) is of particular interest to pathologists. In this case an adenocarcinoma was found growing in a tumor formed of heterotopic gastric mucosa. If the patient had continued to live without an operation, it would, according to the authors, have been only a question of time before the carcinoma had infiltrated the entire heterotopic gastric mucosa and left no trace of its origin in this tissue.

One wonders whether in other cases reviewed in this series carcinoma of Meckel's diverticulum may not have originally begun in heterotopic gastric tissue, further growth of the tumor possibly having made further differentiation of tissue structures impossible. This raises the question whether carcinoma of Meckel's diverticulum may be considered from the same point of view as gastric carcinoma. An accurate account of the percentage of various heterotopic tissues in a large series of Meckel's diverticula would be of importance in this connection. Schaetz, who examined 30 cases, found heterotopic tissue formation in 43 per cent, in 38.5 per cent of which the tissue consisted of gastric mucosa.

If this series of 6 cases of carcinoma and 14 cases of sarcoma of Meckel's diverticulum is again considered, the prevalence of sarcoma so far seems obvious. Considering malignant tumors of the stomach, the relation is exactly the reverse, gastric sarcomas making up about 1 per cent of all malignant gastric tumors. It seems only reasonable, therefore, to conclude that in considering the formation of malignant tumors of Meckel's diverticulum the condition is in no way explained by the types of heterotopic tissues found. In other words, there does not seem to be any exact parallelism between pathologic processes in Meckel's diverticulum and pathologic processes in organs from which the heterotopic tissue of a diverticulum may be considered to have been derived. Still it appears that the heterotopic tissue undoubtedly plays an important rôle in the pathologic process in the organ under discussion.

With the small series of malignant tumors at hand it seems impossible to try to bring out the suggestive symptoms in these cases. In a review of the available clinical data in this series, there are, however, certain points which may be emphasized: A malignant tumor of Meckel's diverticulum may be present without, for a time at least, producing any clinical symptoms, as in the case described by Symmers. When clinical symptoms were associated with malignant tumor of Meckel's diverticulum, the symptoms recorded appeared naturally to fall into two main groups: (1) primary symptoms referable to the presence of the tumor and (2) secondary symptoms referable to the perforation of the diverticulum, leading to localized or diffuse peritonitis or to invagination of the tumor together with the diverticulum.

Unfortunately, in this series the primary symptoms which may reasonably be assumed to be caused by the tumor itself were rather vague. In order to simplify the matter, they may be considered under the following two subheadings: 1. Symptoms of abdominal distress or pain. Abdominal distress appears to have occurred in more than 50 per cent of the cases; it was of an intermittent colicky type and of a moderate degree and was usually located in the right side of the lower part of the abdomen, with frequent projection to the epigastrium. 2. Symptoms caused by the presence of an abdominal tumor. In 5 cases a palpatory finding of a tumor had been made prior to operation. In 2 of these cases the growth presented itself as a pelvic tumor, and in only 2 was it found in the ileocecal region. A palpatory finding which may be of some consequence in localizing the tumor is the occasional tendency for the growth to escape partly or completely from the palpating hand, a phenomenon which suggests the presence of a tumor in the ileum. Regarding secondary symptoms referable to intestinal invagination and ileus, Harkins,[32] after reviewing the literature dealing with intestinal intussusception, concluded that Meckel's diverticulum is a factor in causing intussusception in only 2.5 per cent or less of cases. Considering the great number of Meckel's diverticula reported as compared to the 20 cases of malignant tumors of Meckel's diverticulum reviewed here, one will realize the remote chance of encountering a malignant tumor in a diverticulum that gives rise to intussusception. In this series, in only 1 case (that of Gray and Kernohan) did a malignant tumor lead to intussusception.

Symptoms of localized or diffuse peritonitis were encountered in 4 cases in this series. In 3 of them the diffuse peritonitis resulted from necrosis and perforation of the diverticulum, and the patients died:

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[32] Harkins, H. N.: Intussusception Due to Invaginated Meckel's Diverticulum: Report of Two Cases with a Study of One Hundred and Sixty Cases Collected from the Literature, Ann. Surg. **98**:1070-1095 (Dec.) 1933.

in the fourth case local peritonitis arising from a ruptured appendix was diagnosed preoperatively, and the patient recovered after the operation.

In considering the foregoing symptoms, one is left with the impression that they are of little direct diagnostic importance and that they may also fit a variety of abdominal conditions to be considered at the bedside. The condition under discussion, however, is primarily a surgical problem, and the surgeon may be interested in knowing how great a chance he has of getting the patient to operation even when no clinical diagnosis has been made preoperatively. There is good reason to expect that all patients presenting an abdominal tumor or clinical signs of intussusception and ileus or peritonitis will be considered as needing surgical assistance. On this basis, 9 of the patients in this series would be considered candidates for surgical exploration. In other words, we have reason to expect that at least 50 per cent of patients with malignant tumors of Meckel's diverticulum would be referred for surgical treatment.

In the cases reviewed no evidence of metastasis was ever found. In 2 cases, however (1 of Mathews and 1 of Faust and Walters), there was evidence of recurrence of the tumor, in both cases five years after its removal. This, of necessity, makes for a guarded prognosis.

OLFACTOMETRY IN CASES OF ACUTE HEAD INJURY

PHILIP P. GOLAND, M.D.
NEW YORK

A new quantitative method of testing the sense of smell has recently been described.[1] Whereas by all former methods odors were carried to the olfactory membrane through inhalation or sniffing, by this new method the odorous substance is injected by a process called "blast injection" into one or both nasal passages during cessation of breathing. The known force of the injection takes the place of the inspiratory movement. In this test the volume of air and odor and the pressure of the injection can be measured. "By this test it has become possible to study the threshold of olfactory sensibility, to determine fixed values (olfactory coefficients) for each odor and to gain considerable information regarding the relative importance of the volume and pressure of the olfactory stimulus."[2]

The originators of this method have made practical use of it in the localization of supratentorial tumors of the brain. They have found diminution in unilateral or bilateral olfactory acuity and prolongation of olfactory fatigue dependent on the location of the tumor. These responses appear to be so characteristic that from them alone the position of a tumor interfering with the olfactory mechanism may often be determined.

It was considered advisable to apply this method of olfactometry to the acute traumatic craniocerebral encephalopathies in order to determine the frequency and nature of olfactory disturbances in such injuries. The patients used for the study were found in the skull fracture division of the traumatic surgical service of the Harlem Hospital.

From the Surgical Service of Dr. Louis T. Wright, Harlem Hospital, Dr. Charles S. Cassasa, Director.

[1] Elsberg, C. A., and Levy, I.: The Sense of Smell: A New and Simple Method of Quantitative Olfactometry, Bull. Neurol. Inst. New York 4:5 (March) 1935.

[2] Elsberg, C. A.; Brewer, E. D., and Levy, I.: The Sense of Smell: The Relative Importance of Volume and Pressure of the Impulse for the Sensation of Smell and the Nature of the Olfactory Process, Bull. Neurol. Inst. New York 4: 264 (Oct.) 1935.

The following form was drawn up to simplify the recording of data:

1. Location of fracture and type (if present)..............................
2. Area of contusion or laceration of the scalp..............................
3. Orifice of bleeding ....
   (Presence or absence of spinal fluid)
4. Localizing neurologic signs..............................
5. Probable areas of damage to the brain..............................

	Left	Right	Direct	Contrecoup
Frontal				
Temporal				
Parietal				
Occipital				

6. Red blood cells in the spinal fluid..............................
7. Remarks:
   (*a*) Conscious on admission
   (*b*) Unconscious on admission

The only persons who were considered for study were those who showed no nasal or oral bleeding. (A number of patients were tested by means of the blast injection test in whom it was felt that bleeding had come from about the roof of the nasal cavities. In many instances the olfactory coefficients were elevated. If such bleeding was unilateral, the high olfactory coefficient[3] was usually apparent on this side). The initial test was made when the patient was well enough to sit up in bed and when the sensorium had cleared. A definite procedure was established for all patients for the blast injection test. Before each injection the patient was told to take a deep breath, then to raise the hand as a signal that the breath was being held. After the injection he was instructed to release his breath through the nose. After the blast had been released into the nostril, a short period of time was allowed to elapse before the nose pieces were taken away. In this way there was no confusion whether there was perception of the odor immediately on release of the blast injection or after the expiration when some particles of odor trapped in the nasal cavities might impinge on the olfactory mucous membrane.

It was felt that anterior rhinoscopy was essential in each case before olfactometry was done. Various local conditions of the nose, such as colds and polypi, can produce various degrees of respiratory anosmia. One patient who was sent to the hospital for olfactometry after an intracranial injury complained of anosmia, the onset of which he traced to this injury. Anterior rhinoscopy in this case showed perforation of the nasal septum, most likely syphilitic.

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[3] The smallest number of cubic centimeters of an odor that can be identified when injected into one of the nasal passages during cessation of breathing is called the M. I. O.—the minimum identifiable odor—of the *odorous* substance.

Sixty persons were studied. Thirty-eight seemed to have a head injury uncomplicated by such factors as contusions about the nose, colds and changes in the nasal mucous membrane. None of those with injury to the frontal region of the skull showed any olfactory involvement. One patient with direct injury to the side of the head (a stab by a screw-driver in the left parietal area) showed olfactory involvement on the side of injury. Two patients with injury to the parietal area showed olfactory involvement on the side of the brain which undoubtedly suffered contrecoup injury. Three patients had almost complete anosmia following occipital injuries.

Dr. Elsberg and his co-workers [4] advised the use of coffee and citral for clinical olfactometry. Coffee is considered by them to stimulate the olfactory nerves alone, without having any effect on the trigeminal nerves. Citral likewise, when used in the small volumes needed for the blast injection test, has no effect on the trigeminal nerves.

Three cases are presented in which anosmia occurred after occipital fractures. There was no evidence of nasal bleeding or contusions about the face.

Case 1.—J. L., a Negress aged 48, was admitted to the hospital on Aug. 15, 1936. She was struck by an automobile and was unconscious for approximately one hour, recovering consciousness in the hospital. She was sufficiently rational when seen in the emergency ward to complain clearly of headache in the front and back of the head.

There was a laceration of the occiput. There was no orificial bleeding and no localizing neurologic sign, the only finding being a moderate stupor. Roentgen examination of the skull showed diastasis of the right portion of the lambdoid suture, extending as a fracture to the right middle fossa. Spinal tap done at the time of the patient's admission showed a bloody fluid. The Kahn reaction of the blood was negative.

Olfactometry was done two weeks after the patient's admission. She stated that she had always been able to smell perfectly. She did not complain of a cold in the head during the present examination. Anterior rhinoscopy showed the mucous membrane over both inferior turbinates to be hyperplastic.

The patient had almost complete anosmia; coffee and lemon were not perceived by sniffing. When a can of ether (with its label facing her, which she evidently read) was given her to sniff, she identified the substance within as ether. A sniff test with benzene elicited the response of "smells funny." She was not able to perceive alcohol on sniffing.

The fact that she had answered "ether" after sniffing at the can of ether following the reading of the label showed that she was not malingering. She undoubtedly had a contrecoup injury of the frontal or temporosphenoid lobes with involvement of the olfactory pathways.

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[4] Elsberg, C. A.; Brewer, E. D., and Levy, I.: The Sense of Smell: The Odorous Substances to Be Used for Tests of the Olfactory Sense, Bull. Neurol. Inst. New York 4:286 (Oct.) 1935.

Case 2.—W. G., a Negro aged 40, was admitted to the hospital on June 6, 1936, in a markedly comatose state. There was a hematoma over the occipital region of the skull. There was no orificial bleeding. The pupils were equal and reacted to light and in accommodation. There was no rigidity of the neck. The reflexes were generally exaggerated. There was incontinence of urine. No localizing neurologic signs were elicited.

Roentgen examination of the skull showed comminuted horizontal fractures of the left portion of the occipital squama and of the left parietal, temporal and sphenoid squamae.

Spinal tap at the time of the patient's admission yielded a markedly bloody spinal fluid.

On June 9 there was rigidity of the neck. Kernig's sign was present bilaterally. The spinal fluid was bloody.

On June 18 the sensorium was still clouded. The spinal fluid was pink and turbid. The Kahn reaction of the blood was negative.

On June 20 the patient was up and about the ward.

On June 25 he was discharged.

No olfactory tests were done during the patient's stay in the hospital because of the lack of cooperation. He later returned to the follow-up surgical clinic complaining of inability to smell any odor since the injury to his head.

Olfactometry was done on August 1. Anterior rhinoscopy showed that the nasal septum was deviated to the left.

The patient was unable to perceive the odor of coffee or lemon when given in blast injections of 30 cc. monorhinally. He was likewise unable to perceive these odors by sniffing. He was then told that the substances in the two bottles were coffee and lemon. He thought that he identified the odor of coffee when a blast injection of 30 cc. was given into the right nostril (i. e., after being told that he was going to smell coffee). When told that he was going to smell lemon, he thought that he perceived a lemon odor when a blast of 60 cc. of citral was injected into the right nostril. (Sixty cubic centimeters of pressure can be built up in the bottle by filling it with two loads of 30 cc. of air.) He said that he perceived no odor on sniffing at alcohol, ether and benzene.

Case 3.—E. B., a Negro aged 35, with a history of falling and striking the occiput, was admitted to the hospital on Oct. 22, 1936, the date of injury. He was unconscious on admission. There was no evidence of alcoholism. He reacted to painful stimuli. There was a 2 inch (5 cm.) laceration of the scalp in the right occipital region.

The left pupil was 3 mm. in size and fixed to light, and the right pupil was 2 mm. in size and reacted to light. There were no paralyses and no pathologic reflexes. Spinal puncture yielded a pink fluid. A roentgenogram showed a vertical linear fracture on the right side of the occipital bone.

The following day it was felt that the patient was conscious and rational. The left pupil was still dilated. The patient was discharged on November 2.

He returned on November 16 for olfactometry. The left pupil was still larger than the right, both reacting sluggishly to light. The Kahn test of the blood taken while the patient was in the hospital was 4 plus.

Anterior rhinoscopy showed the nasal mucosa to be congested. The septum was slightly deviated to the left. There was a small amount of mucoid secretion in the rhinal cavities.

The patient complained of tinnitus and difficulty in hearing with the left ear since injury. He also complained of loss of the sense of smell and of a lack of taste to his food.

On one occasion a blast of 30 cc. of coffee was called "stink" when injected into the right nostril. The patient perceived no odors again on further blast injections of coffee or citral into the right or left nostril.

On sniffing at ether, alcohol and benzene with the left nostril he said that he did not smell anything. On sniffing with his right nostril, he said that alcohol smelled like "whisky," benzene smelled "bitter" and ether smelled "strong."

The patient undoubtedly suffered contrecoup injury to the olfactory centers, with possibly greater damage on the left side. The neurologic findings on the left side may substantiate this claim.

MECHANISM OF INJURY

The following mechanism of injury is suggested as the possible etiologic factor in the production of anosmia in the foregoing three cases:

The olfactory nerve arises from a small area of nasal mucous membrane in the upper portion of the nasal septum and the adjacent upper portion of the superior nasal concha. Fine filaments of this nerve perforate the cribriform plate of the ethmoid bone and enter the corresponding olfactory bulb which lies directly on this plate. The central olfactory tract connects the olfactory bulb by means of the lateral and medial olfactory striae with the cortical center for smell, which is located near the tip of the temporosphenoid lobe of the hippocampal gyrus.

Each olfactory bulb is connected with the hippocampal gyrus of its own side by means of the lateral olfactory striae and also with the hippocampal gyrus of the other side by means of the median olfactory striae through the anterior commissure. The lateral olfactory striae are considered to contain a predominately greater number of the secondary fibers and to be more important than the median striae for smell.

When the anterior fossa of the skull is traced backward, it is seen on each side to drop precipitously over the shelving edges of the lesser wings of the sphenoid bone onto the greater wings of this bone. In the recesses between the greater and the lesser wings lie the tips of the temperosphenoid lobes. The lateral olfactory striae and the anterior portion of the hippocampal gyri might conceivably lacerate in a contrecoup injury against these shelving edges of the lesser wings of the sphenoid bone. In a contrecoup injury of the brain the fine olfactory fibers, being exposed on the undersurfaces of the frontal lobes, must come in for a greater degree of injury than if they were buried deeply in the substance of the frontal lobe. Anosmia following occipital injury to the skull might be explained by means of these mechanisms.

Hilton [5] stated in his classic text, "Lectures on Rest and Pain," that:

> When the blow is received at the posterior part of the skull, the whole mass of the brain being driven forwards from the momentum given to it by the blow upon the bones of the skull, the under surface of the anterior part of the brain *rubs over the depressed and elevated* surfaces which constitute the anatomical features of the internal base of the skull.

Collet [6] explained the occurrence of anosmia after occipital blows in the following manner:

> Traumatic anosmia is found especially following injury due to falls on the back of the neck and occasionally following falls on the face. In the first case there is brought about a tearing or pulling of the olfactory fibers through the process of inertia, or perhaps a small bloody effusion compresses the olfactory fibers following the tearing of the vessels which accompany them.

Two anatomic facts appear to him to dominate the pathologic structure of the olfactory nerve. These are: the fineness of the olfactory filaments transversing the olfactory plate and the presence of olfactory (primary) neurons in the nasal mucous membrane.

Ogle [7] first described cases of anosmia following blows or falls on the posterior portions of the head.

Legg [8] reported the case of a man aged 36, who fell on the right posterior parietal region of the skull. He was unconscious for one-half hour and bled from his left ear. Examination of the sense of smell after one week showed perversion but not complete loss of this sense. The author did not know whether to ascribe the loss to a tearing of the olfactory filaments or to involvement of the temporosphenoid lobes of the brain. He believed that his was the sixth case of anosmia following blows to the posterior portions of the head to be mentioned in the literature.

Helsmoortel, Nyssen and Thienpont [9] referred to an investigator, Fugerio, who in 1887 described a case in which auditory and olfactory hallucinations developed following a fall on the occipital region of the skull. Autopsy showed atrophy of the hippocampal convolutions. He ascribed this to contrecoup action. (I have been unable to find this case in the indexes of the medical literature at my disposal.)

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[5] Hilton, John: Lectures on Rest and Pain, ed. 1, London, 1863, p. 25.

[6] Collet, F. J.: Étude statistique et étiologique sur l'anosmie, Rev. d'oto-neuro-opht. **11**:*1* (Jan.) *1933.*

[7] Ogle, William: Anosmia: Cases Illustrating the Physiology and Pathology of the Sense of Smell, Med.-Chir. Tr. **53**:*263,* 1870.

[8] Legg, J. W.: A Case of Anosmia Following a Blow, Lancet **2**:*659* (Nov. 8) *1873.*

[9] Helsmoortel, J.; Nyssen, R., and Thienpont, R.: Les troubles *olfactifs* dans les traumatismes cranio-cérébraux, Rev. d'oto-neuro-opht. **11**:*489* (*July*) 1933.

Bostroem,[10] Laemmele,[11] Helsmoortel, Nyssen and Thienpont[9] and Kindler[12] in recent publications reported anosmia following blows or falls on the occiput.

HIGHER OLFACTORY COEFFICIENTS IN LACERATION OF THE BRAIN

Three cases of injury to the brain are presented. one direct and the other two most likely contrecoup, in which the higher olfactory coefficients were found on the side of injury.

Case 1.—E. F., a Negro aged 23, was struck on the head by a blunt object and rendered unconscious for about one hour. He walked home after regaining consciousness. He since had had severe frontal headaches. He was admitted to the hospital on Aug. 9, 1936, the day of injury, conscious and rational. Examination showed swelling and tenderness of the scalp in the right parieto-occipital region near the vertex. There was no orificial bleeding and no abnormal neurologic signs. Spinal tap on August 10 yielded a bloody fluid, and on August 11, a pink fluid. A roentgenogram of the skull showed a fracture of the right frontal, parietal and occipital bones.

Table 1.—*Results of Blast Injection Tests*

Coffee				Citral			
M. I. O.		Response Elicited		M. I. O.		Response Elicited	
Left	Right	Left	Right	Left	Right	Left	Right
13 cc.	3 cc.	"Not sweet"	"Not sweet"	13 cc.	5 cc.	"Sweet"	"Sweet"

Table 2.—*Results of Stream Injection Tests*

Coffee				Citral			
M. I. O.		Duration of Fatigue		M. I. O.		Duration of Fatigue	
Left	Right	Left	Right	Left	Right	Left	Right
10 cc.	5 cc.	2 min.	1.5 min.	18 cc.	5 cc.	1.5 min.	2.5 min.

Olfactometry was done on August 16, seven days after the patient's admission; anterior rhinoscopy showed hypertrophy of the right inferior turbinate and a septum which was slightly deviated to the right.

Blast injection tests were carried out on August 16 and 18. Coffee and citral were used for both examinations, and the minimum identifiable odor was greater on the left than on the right (table 1).

Stream injection tests[13] were carried out on August 18 (table 2).

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[10] Bostroem, A.: Ueber traumatische Hirnschädigungen, Wien. klin. Wchnschr. **43**:129 (Jan. 30) 1930.

[11] Laemmele, H.: Ueber Geruchsstörungen und ihre klinische Bedeutung, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **130**:22 (Oct. 8) 1931.

[12] Kindler, W.: Geruchsstörungen nach Schädelverletzung in medizinischer und sozialer Bedeutung, Med. Welt **10**:150 (Feb. 1) 1936.

[13] Elsberg, C. A.: The Sense of Smell: Olfactory Fatigue, Bull. Neurol. Inst. New York **4**:479 (Dec.) 1935.

The patient undoubtedly suffered a contrecoup laceration of the left frontal lobe and possibly of the left temporal lobe, the side which gave the higher minimum identifiable odor.

CASE 2.—J. B., a Negro aged 40, was admitted to the hospital on March 25, 1936. He was found lying on the sidewalk in an unconscious state and suffering from alcoholism.

Physical examination showed an unconscious man with a contusion of the scalp in the left parietal area. The left pupil was larger than the right and did not react to light. There was hemiplegia on the left (including facial paralysis of the upper motor neuron type). The hemiplegia proved later to be hemiparesis and was gone the following day.

There was no orificial bleeding. Roentgen examination of the skull gave negative results. Spinal tap at the time of the patient's admission yielded a bloody fluid; six days later bloody fluid was again obtained.

The patient regained consciousness on the following day. He was confused and irrational for a period of about two weeks.

Olfactometry was done on April 22. The left pupil at this time was still larger than the right and reacted sluggishly to light. The patient complained of dizziness and weakness. Anterior rhinoscopy showed the septum to be deviated to the left, with a spur formation in its lower portion, on the left. Blast injection tests were carried out (table 3).

TABLE 3.—*Results of Blast Injection Tests*

Coffee				Citral			
M. I. O.		Response Elicited		M. I. O.		Response Elicited	
Left	Right	Left	Right	Left	Right	Left	Right
6 cc.	10 cc.	"Coffee"	"Coffee"	4 cc.	20 cc.	"Mint"	"Mint"

The patient was discharged before stream injection tests could be carried out.

The higher minimum indentifiable odor was found on the side on which injury to the cerebrum had produced left hemiparesis (i. e., involvement of the right side of the brain).

CASE 3.—M. G., a Negress aged 22, was admitted to the hospital on July 11, 1936, in a semiconscious and wildly excited state. The history obtained from the family was that the patient had been stabbed in the head with a screw-driver.

Physical examination revealed a small laceration of the scalp in the left parietotemporal area. The right pupil was larger than the left. The patient was unmanageable and had to be controlled by intravenous injection of sodium amytal.

Spinal tap on July 11 and on July 13 yielded a bloody fluid. On July 16 the patient became quieter and began to regain consciousness.

When she became rational it was seen that she had a motor aphasia for speech. She later complained that she could not see things to the right of her. Examination revealed right lateral homonymous hemianopia.

Olfactometry was attempted on July 28; anterior rhinoscopy showed that the nasal septum was slightly to the left. Because of the aphasia, interpretation of responses were confusing. An attempt was made the following day with similar confusion. The patient was discharged on August 3.

She returned on October 16 for examination. Olfactometry by blast injection was done at this time (table 4). There were still slight residuals of the motor aphasia.

An attempt was made to recheck the values by testing with each substance. The patient evidently began to tire of what she called an "unnecessary test." She said she smelled the substances when only from 2 to 4 cc. would be injected into each nostril. Such secondary attempts were stopped, and the patient was requested to return the following day. She did not return.

The marked difference in the minimum identifiable odor on the two sides must furnish, however, some validity to the initial tests. It would have been interesting to carry out stream injection tests to determine the duration of olfactory fatigue because of the likewise high values for the minimum identifiable odor on the right side.

It is likely in this case that there was injury to the left temporal lobe of the brain with involvement of Broca's area, the uncus and the left optic tract lying mesial to it.

TABLE 4.—*Results of Blast Injection Tests*

Coffee				Citral			
M. I. O.		Response Elicited		M. I. O.		Response Elicited	
Left	Right	Left	Right	Left	Right	Left	Right
30 cc.*	15 cc.	"Coffee"	"Coffee"	30 cc.*	15 cc.	"Sweet"	"Sweet"

* The patient did not perceive any odor when 30 cc. had been injected except on one occasion.

Ogle[7] reported a case of aphasia and agraphia following a fit. The aphasia was not so complete as to prevent the patient from making himself understood; there was no paralysis present. This patient was able to smell much better with his right nostril than with his left.

This investigator also described the case of a boy aged 12 years who suddenly lost power in his right side and fell without losing consciousness. He had a fit a few hours later which left him with partial aphasia and incomplete hemiplegia on the right side. He completely lost the sense of smell in the left nostril.

This writer expressed the belief that the lesions producing the aphasia in the two cases implicated also the fibers of the "external root of the olfactory bulb."

Such lateralization (ipsilateral predominance) of the sense of smell has been clearly indicated in the work of Elsberg[14] in the localization of suprasellar tumors and tumors of the frontal lobe of the brain.

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14. Elsberg, C. A.: The Sense of Smell: The Value of Quantitative Olfactory Tests for the Localization of Supratentorial Tumors of the Brain; a Preliminary Report, Bull. Neurol. Inst. New York 4:511 (Dec.) 1935; The Sense of Smell: The Localization of Tumors of the Frontal Lobe of the Brain by Quantitative Olfactory Tests, ibid. 4:535 (April) 1936.

In the limited number of cases of injury to the side of the head which were presented in this article, a lateralization (ipsilateral predominance) of the sense of smell was indicated.

SUMMARY

Olfactometry was done on sixty patients with acute trauma to the head.

In thirty-eight patients the injury was uncomplicated by such factors as contusions about the nose, colds and changes in the nasal mucous membrane.

Three of the thirty-eight showed almost complete anosmia following injury to the occipital region of the skull.

Injuries about the anterior portions of the head seem to play a secondary rôle in producing disturbances of the sense of smell (i. e., without local injury to the nose or fractures through the cribriform plate).

This loss of the sense of smell following injuries to the back of the head or neck is usually ascribed to contrecoup action on the olfactory fibers lying on the undersurfaces of the frontal lobes.

A new mechanism of injury is suggested in which the lateral olfactory striae and the tips of the temporosphenoid lobes are injured against the lesser wings of the sphenoid bone.

Three cases are presented in which there were injuries to the side of the head. The patient who suffered from direct injury to the parietal and temporal lobes of the brain had higher olfactory coefficients on the side of injury. The two who had contrecoup involvement of the brain showed the higher olfactory coefficients on the side of the injury.

CONCLUSION

1. Falls or blows on the back of the neck and occiput seem to be predominant in producing disturbances or loss of the sense of smell. The occurrence of anosmia after such injuries is not infrequent.

2. Injuries to the front of the head (i. e., without local injury to the nose or fractures of the anterior cranial fossa or cribiform plate) play a secondary rôle in producing disturbances of the sense of smell.

3. Injuries to the side of the head may produce disturbances of the sense of smell. In the limited number of cases presented the higher olfactory coefficients were obtained on the side of the injury.

SIXTY-FOURTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Heredity in Congenital Dislocation of the Hip.—By the reproduction of a set of 10 family trees, Faber [1] shows not only that true congenital dislocation of the hip (25 cases) occurs in these families but that dysplasia of the hip joint (73 cases), oblique acetabulum and subluxation are found three times as often as dislocation. This indicates that the taint is four times as strong as would be suspected if only dislocations were sought. Furthermore, parents with simple dysplasia may have children with true dislocation. While true dislocation in this series was much more frequent in the female (5 to 1) than in the male, if one includes the cases of dysplasia the ratio is 1.55 to 1. The father as well as the mother in an affected family may transmit dysplasia or true dislocation. Furthermore, it is probable that unaffected persons in such a family may act as "carriers."

[ED. NOTE.—A study of the distribution of monarticular osteoarthritis of the hip (which is probably often the clinical end-result of such dysplasia) may reveal a long suspected correlation.]

This report of progress is based on a review of 126 pages selected from 181 titles related to orthopedic surgery, which appeared in the medical literature approximately between March 1, 1937 and July 2, 1937.

[1] Faber, A.: Ztschr. f. Orthop. 66:140, 1937.

Arthrography in Congenital Dislocation of the Hip.—Leveuf and Bertrand[2] have frequently found a lengthened articular capsule with a closed portion in the middle in cases of congenital dislocation of the hip. This defect in the capsule is not readily determined clinically, although roentgenograms will show a wide separation of the head of the femur and the acetabulum. By the use of colloidal thorium dioxide, neo-iopax and other radiopaque substances, the authors were able to demonstrate the narrowing or closure of the articular capsule in roentgenograms. Ten cubic centimeters of a 30 per cent solution of the opaque substance was injected into the hip joint, the neede being introduced anteriorly to the head of the femur.

DEVELOPMENTAL DISTURBANCES

Osteitis Fibrosa Disseminata, Areas of Pigmentation and Precocious Puberty in Females.—Five cases of this syndrome are reported by Albright and his co-workers,[3] and illustrations of the pigmented areas and diagrams of the areas of osseous involvement are presented. In addition, reports of 9 strikingly similar cases and 5 suggestively similar ones were found in a search of the literature; the diagnoses in these cases included neurofibromatosis, juvenile Paget's disease, xanthoma, osteodystrophia fibrosa and osteitis fibrosa generalisata. The characteristics of the syndrome are: (1) changes in the bone, (2) brown pigmented areas and (3) endocrine dysfunction. The changes in the bone are spotty in distribution and consist of multiple localized cystlike areas often associated with circumscribed areas of increased density. It is remarkable that the changes show a tendency to be unilateral, or at least regional, i. e., in one entire extremity. The epiphyses often escape involvement when the entire remainder of the shaft is involved. Early fusion of the epiphyses is the rule, associated with precocious bone age, i. e., premature appearance of ossification centers. Microscopic examination of the areas involved usually reveals a notable absence of osteoclasts. Since the surrounding areas of bone are not affected, the condition should be classified as osteitis fibrosa localisata as opposed to osteitis fibrosa generalisata; however, because the lesions are multiple, the designation osteitis fibrosa disseminata has been used. Further differentiation from hyperparathyroidism is based on the facts that the values for serum calcium and inorganic phosphorus are within normal limits and the urinary excretion is not increased. Increased values for serum phosphatase may be found in cases in which there are advanced changes in the bone. Pigmentation is patchy and occurs most frequently over the sacrum, buttocks and upper part of the spine. The patches do not appear to have the same distribution as the cutaneous nerves. The distribution of the osseous and cutaneous lesions suggests an embryologic or a neurologic disturbance. The former would be more likely if the pigmentation were due solely to melanoblasts of mesodermal origin. Though the distribution of the pigmented areas is such as to suggest a mesodermal origin, the histologic evidence indicates that most of the melanoblasts are of ectodermal origin. This would seem to require an embryologic disturbance affecting both the ectoderm and the mesoderm. The unilateral character of the syndrome is similar to that observed in Ollier's dyschondroplasia, in which there are multiple unilateral enchondromas. Precocious puberty occurs only in the female, suggesting the hypothesis that this part of the syndrome is due to a disturbance in the follicle-stimulating hormone of the pituitary gland. The disease in its complete form must be rare. It is suggested, however, that it may occur in incomplete forms, and in cases in which hyperparathyroidism is suspected to be present this must always be considered. A prognosis of serious disability from fractures seems justified. Roentgen irradiation of the local lesions or of the pituitary gland or of the region of the parathyroid glands has been attempted, but with inconclusive results.

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[2] Leveuf, J., and Bertrand, P.: Presse méd. **45**:437, 1937.

[3] Albright, F.; Butler, A. M.; Hampton, A. O., and Smith, P.: New England J. Med. **216**:727, 1937.

Pathogenesis of Certain Growth Disturbances.—Schneider[4] believes that the aseptic osteocartilaginous necrosis observed in children, e. g., Legg-Perthes' disease, is explained by a disturbance in nutrition. He reviews the various theories proposed in the literature and concludes that three possibilities are present: (1) a vitamin deficiency, (2) an endocrine disturbance with interference with the storage and saturation of vitamins and (3) loss of vitamins following infection. He reviews a large number of personally observed cases in which the blood serum was deficient in vitamin A. He shows the relationship of hypothyroidism and hyperthyroidism to the storage of vitamin A and the gradual injury that may occur to the cartilage and bone following loss of this vitamin.

A possible therapeutic approach through the investigation of vitamin A deficiency is suggested in addition to the commonly employed symptomatic mechanical therapy.

Köhler's Disease of the Tarsal Scaphoid.—Smets,[5] of Brussels, concludes from a clinical study and from a review of the cases reported in the medical literature that so-called Köhler's disease is a normal variation in ossification. His reasons for this are: 1. The lesion is usually found on both sides. 2. In most cases there are no symptoms, and the condition is an incidental roentgenographic finding. 3. The lesion heals spontaneously. 4. Usually alterations in ossification can be found in other parts of the body. 5. There is a familial tendency to this condition which is occasionally shown in twins. At times, as the author demonstrates, this variation in ossification is a generalized phenomenon.

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[4] Schneider, E.: Arch. f. klin. Chir. **188**:91, 1937.

[5] Smets, W.: Bull. Soc. belge d'orthop. **7**:65, 1936.

OSSEOUS CHANGES IN CERTAIN DISEASES

Osseous Changes in Sickle Cell Anemia.—Diggs and his co-workers[6] conclude from the study of 30 cases of sickle cell anemia, some of which were studied microscopically, that the gross, microscopic and roentgenographic appearances of the bones indicate that the bone marrow is primarily involved. Two factors appear to be working in opposite directions. One factor is hyperplasia, which tends to increase the volume of the marrow at the expense of bone, and the other is sclerosis, which tends to replace the marrow and to substitute osteoid tissue or new bone. The excessive and abnormal growth activity of the marrow has, as a rule, no significant effect on the bony cage within which it is confined, and such effects as it does have are maximal in the bones which are normally engaged in the formation of blood cells, such as the skull and the cancellous bones of the trunk. In these bones osteoporosis is dominant. In the long bones in which normal hematopoiesis does not occur sclerosis is dominant. The combination of marrow-expanding and marrow-replacing processes leads, if the patient lives long enough, to gross anatomic derangements in the structure of the bone.

Osseous Changes in Leukemia.—Connor[7] states that the roentgenographic appearance of bones of patients suffering from leukemia may be similar to that of bones of persons with osteomyelitis. The differential diagnosis is dependent on a study of the blood.

Changes in the Growing Skeleton After the Administration of Bismuth.—The roentgenographic changes produced in the skeleton of infants and children by bismuth are described by Caffey,[8] and the similarity of these changes to those produced by lead is pointed out. The most conspicuous microscopic changes are: (1) an increase in the calcified cartilaginous matrix in the zone of primary calcification, accompanied by a decrease in the endosteal bone usually present in this region, and (2) later active deposition of bone in the deeper parts of the lesion, which, owing to the increased cartilaginous framework, results in a zone containing a larger amount of bone than is normal. Minor differences in the microscopic changes produced by lead and bismuth are described.

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[6] Diggs, L. W.; Pullian, H. N., and King, J. C.: South. M. J. 30:249, 1937.

[7] Connor, C. L.: Am. J. Cancer **29**:20, 1937.

[8] Caffey, J.: Changes in Growing Skeleton After Administration of Bismuth, Am. J. Dis. Child. **53**:56 (Jan.) 1937.

Osseous Changes in Recklinghausen's Neurofibromatosis.—Norgaard,[9] of Copenhagen, reviews the osseous changes observed both in personally observed cases of Recklinghausen's neurofibromatosis and in those cases reported in the literature. These changes may be of importance in the differential diagnosis when the usual symptoms of the disease are not very evident. Kyphoscoliosis is present in most of the cases due to osseous changes, which resemble those seen in osteomalacia. Periosteal cysts are frequently seen. There may be increased or diminished growth of parts of the skeleton. Roentgenograms illustrating these osseous changes accompany the article.

OSTEOMYELITIS

Acute Osteomyelitis.—Sorrel,[10] in a discussion of the treatment of acute osteomyelitis, states that the immunologic forms of therapy offer little at present. Osteomyelitis, with its staphylococcic septicemia and localization in bone, is different from many other infections. Antibodies are produced only slowly or not at all. None of the methods so far used —vaccine therapy, transfusions of blood from immune subjects, bacteriophage or staphylococcus antitoxin—have decreased the use of surgical treatment for osteomyelitis. Except in cases of staphylococcic septicemia with few symptoms referable to the bone, immediate surgical intervention is indicated. The type of operation will depend on the nature of the osteomyelitis.

[Ed. Note.—While little benefit has been observed from the immunologic forms of treatment, there is a tendency toward greater conservatism in treatment.]

Diaphysial Resection in Osteomyelitis.—Sorrel[11] reports the results of resection of the diaphysis in 32 cases of acute osteomyelitis. He feels that the operation has a definite place in cases of acute widespread osteomyelitis in a single bone in which the patient is gravely ill and in which in all probability the bone has become necrotic over a large area. He reserves simple incision for subperiosteal abscess and simple opening of the bone for a localized central abscess. Of 32 patients subjected to diaphysectomy, chiefly of the tibia and the femur, 4 died, 6 could not be traced and 1 underwent operation too recently for comment. The remaining 21 patients were completely cured, with regeneration of the bone; growth proceeded normally, and normal function was restored. In 4, pseudoarthrosis resulted, necessitating later grafting of the area.

[Ed. Note.—Diaphysectomy is rarely advisable except in bones that are not necessary for function. The danger of nonregeneration is too great.]

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9. Norgaard, F.: Acta radiol. **18**:460, 1937.
10. Sorrel, E.: Cir. ortop. y traumatol., Habana **5**:3, 1937.
11. Sorrel, E.: Bull. Soc. belge d'orthop. **9**:319, 1937.

Syphilitic Osteomyelitis.—Two cases of syphilitic osteomyelitis are reported by Westermark and Hellerström[12] in which a preliminary diagnosis of osteogenic sarcoma had been made. The first patient, aged 25, had a warm pulsating tumor of the soft part over the anterior aspect of the left tibia of six months' duration. Roentgenograms showed a destructive lesion, not sharply outlined, with spicule formation in the upper part of the tibia The Wassermann reaction was positive, and healing occurred under antisyphilitic therapy. The second patient, aged 33, had a gradually increasing swelling on the left tibia, with pulsation and local heat. Roentgenograms showed a destructive process with spicule formation. In this case, also, the Wassermann reaction was positive, and healing took place under antisyphilitic treatment. The ability of syphilis to simulate an osseous neoplasm makes a careful study imperative.

TUBERCULOSIS

Pott's Disease in Adults.—McKee[13] compares the end-results in cases of tuberculosis of the spinal column in which conservative methods of therapy were employed with those in which operative fixation was done. Good clinical results were obtained in 70 per cent of the former, with late abscess formation in only 4 per cent, while such results were obtained in only 32 per cent of the latter, with late abscess formation in 40 per cent. McKee concludes that a graft should serve as a local internal splint and should be employed only after consolidation has taken place.

[ED. NOTE.—The efficacy of spinal fusion is dependent largely on the treatment of the patient for the systemic disease.]

Tuberculosis of the Knee.—Hellner[14] analyzes 87 cases of tuberculosis of the knee seen at the surgical clinic of Munster between 1925 and 1936. In 20 cases tuberculosis was thought to be present, but the condition was later proved to be nontuberculous. Diagnosis was established by the clinical course, inoculation of guinea-pigs or excision of tissue. No method of diagnosis was found applicable to all cases. Exploratory excision of tissue did not have an unfavorable influence in any case. Conservative treatment, in the author's opinion, is not justified except in cases of early tuberculous hydrops in which motion is still present and does not lead to cure. Resection of the joint in cases of fungoid tuberculosis and amputation in those cases in which extensive secondary infection is present are the treatments of choice. No figures are given for the end-results.

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[12] Westermark, N., and Hellerström, S.: Acta radiol. **18**:422, 1937.

[13] McKee, G. K.: Brit. J. Surg. **24**:456, 1937.

[14] Hellner, H.: Arch. f. klin. Chir. **188**:215, 1937.

Operative Treatment of Tuberculosis of the Knee Joint.—Tregubov's [15] conclusions concerning the treatment of tuberculosis of the knee joint are based on the results obtained in 609 cases during the period between 1921 and 1936, in 147 of which surgical measures were employed. He feels that the best results are obtained by operative treatment. Although adolescents and adults are the most suitable subjects for operation, excellent results have also been obtained in elderly persons. The period of abatement of the tuberculous process is the best time to perform the operation, which should be a simple one, aiming chiefly at the formation of ankylosis, although the foci in the bone should be thoroughly removed by curettement and the cavity filled with bone chips. It is important to fix the knee in a position of slight flexion. A plaster cast is applied from the pelvis to the toes. At the end of approximately six weeks the patient is permitted to walk on crutches and to bear weight on the affected leg. Three months after the operation the plaster bandage is shortened. During the following three months the patient bears weight freely on the leg. At the end of this time a removable cast is applied. Of 147 patients operated on, 2 died, 1 from accidental infection and the other from tuberculous meningitis. In both cases, however, the process in the knee joints healed. Of the remaining 145 patients, only 55 appeared for examination. Forty-six of these obtained good results and have returned to a normal life. In 2, shortening amounted to 7 cm., but in the others it averaged between 3 and 4.5 cm. The author strongly condemns the so-called nailing operations.

On the basis of a follow-up study of patients treated in a tuberculosis sanatorium, 75 by conservative measures and 30 by fusion, Lampadius [16] advocates conservative therapy in preference to operation. His conservative treatment consists of rest, diet and the use of a plaster bed. Fresh air rather than direct sunlight is stressed. All but 2 of the patients treated in this manner improved. Healing occurred in 28 with a gibbus and in 37 without a gibbus. Diagnosis was confirmed by roentgenographic examination for the most part, and the course was followed by determinations of the sedimentation rate. At the time of reexamination there were 30 patients on whom operative treatment had been used (Albee's technic). In addition to this group, 4 had died of the operation and 6 had died since discharge from the hospital (3 of unknown causes). The author states that in the 30 patients the "good and bad results balanced."

[Ed. Note.—The statistical material does not lend itself to satisfactory comparison as presented in the paper. No systematic tabulation indicative of the age, duration, presence of tuberculosis elsewhere or the clinical severity of the lesion in the different groups is available.]

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[15] Tregubov, S.: J. Bone & Joint Surg. **19**:734, 1937.

[16] Lampadius, H.: Ztschr. f. Orthop. **66**:89, 1937.

THE BACK

Spinal Deformity Following Tetanus.—Roberg [17] presents the results of a study of all of the factors which may lead to spinal deformity following tetanus. Sixty-three cases, comprising all of those reported in the literature up to the present, were reviewed. Photographs, roentgenograms and charts have been included. Kyphosis of the vertebral column may follow tetanus with or without demonstrable fracture of the vertebral body. Therefore, initiating this deformity is the contraction of certain muscle groups during tetanic convulsion. Although there is a greater tendency for vertebral fracture to occur in adults, the majority of cases of posttetanic kyphosis occur in adolescents of an age corresponding to those affected with juvenile kyphosis. Posttetanic spinal deformity in adults is the result of a peculiarly severe and prolonged attack of tetanus.

Lesions of the Intervertebral Disk.—Barr [18] reports 40 cases in which lesions of the intervertebral disk were verified at operation. The symptoms and signs of rupture of the intervertebral disk depend on the location of the lesion. Lesions in the lumbar region produce a characteristic clinical syndrome. In 26 of the cases in the reported series the involved disk was between the fourth and the fifth lumbar vertebra. The youngest patient was 20 years of age and the oldest 58. Thirty-five of the patients were males. Thirty patients gave a history of trauma. The chief symptom was pain along the sciatic nerve and its branches. and in 34 cases the pain was unilateral. There was a list of the lumbar portion of the spine in 26 cases. Reflexes were normal. Sensory disturbances were present in 17 cases. Roentgenographic study showed no narrowing of the intervertebral disk in 25. Roentgenographic examination following the injection of iodized poppy-seed oil 40 per cent was carried out in 39 cases and showed total block in 5, partial in 30 and a questionable filling defect in 1. Lumbar puncture showed an elevated total protein content in the spinal fluid in 35 cases. The dynamics of the spinal fluid were normal in 36. The findings at laminectomy varied greatly. The extruded nucleus pulposus was usually removed without undue difficulty. Spinal fusion was performed on 12 patients at the time of laminectomy to insure greater stability where articular facets had been removed. Twenty-nine patients were completely relieved of pain; 2 had a disabling motor weakness or paralysis, and 2 had died, 1 from uremia and 1 from pneumonia. The remaining patients were not followed sufficiently long for comment.

Chronic Traumatic (Postural) Destruction of the Lumbosacral Intervertebral Disks.—Williams [19] believes that mechanical alterations of the lower part of the spine which cause an uneven distribution of weight on the intervertebral disks may produce early pathologic degeneration of that portion of each disk which is under abnormal pressure. When the patient is in the erect position this pressure is exerted only on the posterior and lateral margins of disks. The symptoms usually occur between the ages of 30 and 40 and consist of a relaxed attitude and poor muscular tonus and a history of fatigue and pain, the latter being aching in character. The pathologic process is manifest by degenerative changes involving the annulus fibrosus and the nucleus pulposus and by subluxation of the facets, with resulting degenerative arthritic changes. Roentgenographic studies reveal pelvic obliquity, narrowing of the lumbosacral joint space, subluxation of the lumbosacral facets and frequently hypertrophic lipping and sclerosis involving the articulations and occasionally the vertebral bodies. Treatment varies according to the age of the patient and the severity of the symptoms. Pelvic obliquity should be compensated by adding a lift to the heel of the shoe. Exaggerated lordosis of the lumbosacral portion of the spine in a man under the age of 50 and in a woman under the age of 40, whose roentgenograms reveal narrowing of the posterior margins of the disks and whose symptoms are chronic, is treated by postural exercises. All foci of infection should be removed and high heels replaced by medium or low heels. When the symptoms are acute, a plaster jacket is applied with the patient in a standing position and with the spine flexed so that the lordosis is eradicated. This jacket is later replaced by an orthopedic corset. When all symptoms have disappeared, postural exercises are instituted. In an older patient, postural exercises and a brace to support the lower part of the spine and to eradicate the lordosis are indicated. When the deformity fails to respond to such conservative treatment, surgical measures should be employed.

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[17] Roberg, O. T., Jr.: J. Bone & Joint Surg. **19**:603, 1937.

[18] Barr, J. S.: J. Bone & Joint Surg. **19**:323, 1937.

[19] Williams, P. C.: J. Bone & Joint Surg. **19**:690, 1937.

Operative Treatment for Pain Low in the Back.—After reviewing the various types of operations which have been described for relief of pain low in the back, Compere[20] states that the majority of patients with this type of pain can be relieved without operative intervention. Operation should be performed only after the diagnosis has been accurately established and the presence of an osseous neoplasm or a neurologic lesion has been excluded. Definite indications for operative treatment include tuberculosis or chronic sclerosing osteomyelitis of the lumbosacral or sacro-iliac joints, primary malignant neoplasms, lesions of the spinal cord, spondylolysis or spondylolisthesis. The operation is contraindicated in patients with chronic infectious arthritis, in patients with a psychiatric background and in those seeking financial compensation for injuries. Compere believes that operation is justified for chronic strain low in the back in the absence of definite roentgenographic evidence of a local pathologic process if conservative therapy has failed to bring relief and the patient has to do manual labor to earn a living. The author considers arthrodesis the operation of choice. If sciatic neuritis is present, excision of the articular facets on each side between the fourth and the fifth lumbar vertebrae and the fifth lumbar vertebra and the sacrum is advised.

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[20] Compere, E. L.: J. Bone & Joint Surg. **19**:749, 1937.

CHRONIC ARTHRITIS

Evaluation of Diagnostic Tests in Rheumatoid Arthritis.—Short and his co-workers [21] review the various laboratory procedures employed in the diagnosis and evaluation of chronic arthritis. The blood sedimentation test was found to be positive in 92 per cent of 49 patients with active rehumatoid arthritis. The Schilling count was helpful in 87 per cent. Positive readings were obtained with the Vernes test in 58 per cent, and the streptococcus agglutination test was positive in 53 per cent. The authors conclude that for ease of performance and accuracy the blood sedimentation test is the most satisfactory test for the recognition and evaluation of rheumatoid arthritis.

VASCULAR DISTURBANCES OF THE EXTREMITIES

Value of Sympathectomy in the Treatment of Vascular Disease.—The results of sympathectomy in Raynaud's disease and thrombo-angiitis obliterans are discussed by Smithwick.[22] The various operative approaches recommended and the stages of the diseases at which optimum results may be obtained from operation are described in detail. In summary, the author states that preganglionic section in cases in which there are marked vascular spasms of the extremities, e. g., in Raynaud's disease, has given satisfactory results which could not be obtained by ganglionectomy. In certain cases of thrombo-angiitis obliterans peripheral nerve block is satisfactory, and in a smaller number preganglionic section gives the desired results.

Treatment of Diabetic Gangrene.—Samuels [23] advocates complete rest with the affected extremity in a horizontal position for the treatment of impending diabetic gangrene. Superficial infections should be treated by gentle irrigation through sterile dressings. The natural heat of the limb should be preserved, but excessive heat applied externally does harm. A 2 or 3 per cent hypertonic saline solution should be given intravenously. The author observed no improvement from the use of negative pressure or from ganglionectomy or sympathectomy. Ringworm infections should be treated thoroughly, since they produce lesions from which other infections start. The indications for amputation are spreading gangrene or spreading infection. The author prefers for amputation a simple circular incision in the lower third of the femur with immediate closure of the stump.

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[21] Short, C. L.; Dienes, L., and Bauer, W.: Rheumatoid Arthritis: Comparative Evaluation of Commonly Employed Diagnostic Tests, J. A. M. A. **108**: 2087 (June 19) 1937.

[22] Smithwick, R. H.: New England J. Med. **216**:141, 1937.

[23] Samuels, S. S.: Surgery **2**:225, 1937.

THE SHOULDER

Painful Shoulder.—Ferguson[24] reviews the treatment of soft tissue lesions involving the subacromial or subdeltoid bursa and the supraspinatous tendon in 200 patients. The following lesions are discussed: (1) acute traumatic bursitis, (2) acute bursitis with calcifications, (3) subacute bursitis with calcification, (4) chronic bursitis and (5) tendinitis or obliterative bursitis. For the treatment of acute traumatic bursitis, the author uses immobilization of the shoulder by means of strapping with adhesive tape, an illustration of which is given in the text. After two or three days he uses moist or dry heat. Immobilization should be continued for a week or ten days, followed by exercises which gradually increase the range of motion until normal function is reached after a period of three or four weeks. The author believes that the prognosis is good provided immobilization is maintained long enough. Treatment for acute subdeltoid bursitis with calcification consists mainly of relieving the tension in the bursa by incision, procaine hydrochloride being used to obtain anesthesia. With the relief of the tension, the patient experiences immediate comfort. The incision is enlarged, and as much of the calcified material as possible is removed with a curet. A simple pressure dressing is applied, and a sling is adjusted. Immediate relief is followed by recovery without disability in one or two weeks. Subacute bursitis with calcification presents a different roentgenographic picture, for the areas of calcification are not usually so large or so dense as those in acute bursitis and are located on top of the greater tuberosity rather than along its lateral edge. The pathologic process consists of an area of calcification in the floor of the bursa. Treatment should be conservative. Operation is contraindicated. Baking and diathermy are effective in relieving the pain in about half the cases, but in those cases in which relief is not obtained by such measures injections of from 20 to 30 cc. of 1 per cent solution of procaine hydrochloride in the region of the bursa are often effective. After the acute symptoms have subsided, active exercises within pain limits are of most value. The prognosis for eventual recovery is good. The roentgenographic picture of chronic bursitis consists of changes in the greater tuberosity, with excrescences and small defects at the insertion of the supraspinatus tendon on the greater tuberosity. Trauma may also cause the development of villi. The treatment is divided into conservative and operative. Conservative treatment consists of rest and the application of heat. However, in a few patients in whom the symptoms persist, incision of the bursa and excision of the offending villi or excrescences are advised. In Ferguson's hands this method of treatment was successful in 4 cases. The prognosis is usually good. As a rule, under conservative therapy relief from symptoms may be obtained in from three to four weeks. When symptoms persist beyond this time, operation is indicated, with the prospect of relief from symptoms in another three or four weeks. In cases of tendinitis or obliterative bursitis treatment with heat and rest is slow and often discouraging. A second method has proved more successful, namely, the injection of from 20 to 30 cc. of 1 per cent solution of procaine hydrochloride into the region of the subdeltoid bursa. After the injection, manipulations are carried out carefully. First internal and external rotation are done, followed by circumduction at the shoulder, with a gradually increasing range of motion. During the manipulation there may often be a palpable and even an audible snap. If the manipulation is too painful, sometimes a second injection of procaine hydrochloride is necessary. In some cases the normal range of motion may not be recovered for from six to twelve months.

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[24] Ferguson, L. K.: Ann. Surg. **105**:243, 1937.

Alar Scapula.—Berkheiser and Shapiro [25] report 4 cases of alar scapula resulting from traumatic paralysis of the serratus anterior muscle. Injury to the long respiratory nerve of Bell was caused by violent pulling movements (lifting window, scrubbing, etc.) of the upper part of the arm in each instance. For treatment, the arm and thorax were incased in plaster with the elbow flexed 90 degrees and the arm externally rotated 180 degrees and abducted 90 degrees for three months. In this position the scapula was pressed against the wall of the chest, and the serratus anterior muscle was relaxed. Complete recovery was observed in these cases.

THE NECK

Cervical Rib and Scalenus Anticus Syndrome.—The term "scalenus anticus syndrome" has been suggested for a condition characterized by pain, circulatory disturbances and trophic changes in the upper extremities resulting from movements of the head, neck and shoulder girdle, in the absence of roentgenographic evidence of a cervical rib.[26] The clinical picture presented by cervical ribs is very similar. The size of a cervical rib is no index to the severity of the symptoms it produces since the determining factor is its relation to adjacent structures, the most important of which is the scalenus anticus muscle. It is this muscle that compresses the subclavian artery and the brachial plexus against the cervical rib. The symptoms of compression of the brachial plexus and subclavian artery are usually pain, atrophy, numbness or circulatory changes, consisting of cyanosis, ulcers and rarely gangrene. Although the pain may be more or less continuous, it is invariably exaggerated by rotation of the head or by a forcible downward pull of the shoulder. Circulatory symptoms may manifest themselves by a dusky hue of the arm and hand as compared with the opposite side. Diminution in volume of the radial pulse is common. The pulse can be decreased or obliterated by having the patient elevate the chin or rotate the head to the affected side on inspiration. Treatment for the relief of symptoms of cervical rib and of the scalenus anticus syndrome are the same. The operation which has proved of the greatest value for both conditions is division of the scalenus anticus muscle through an anterior approach. In cases of cervical rib, after the muscle is divided the cervical rib is examined, and if it is causing no pressure from behind further operative treatment is unnecessary. However, if the cervical rib or tendinous attachment to the first rib seems to be compressing the brachial plexus from behind, a portion of the rib and tendon can be removed. Six cases of the scalenus anticus syndrome are reported.

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[25] Berkheiser, E. J., and Shapiro, F.: Alar Scapula: Traumatic Palsy of Serratus Magnus, J. A. M. A. **108**:1790 (May 22) 1937.

[26] Craig, W. M., and Knepper, E. A.: Ann. Surg. **105**:556, 1937.

POSTURE

Postural Deformities of the Anteroposterior Curves of the Spine.—Wiles,[27] in the current Hunterian lecture, reviews the neuromuscular physiology of erect posture. He points out that ligaments limit the extremes of motion only and play no part in the normal regulation of posture. In most instances of faulty posture the error lies in postural reflexes and rarely in muscular weakness. He lists the chief etiologic factors producing postural deformities as undernutrition, rapid growth and psychologic maladjustment. A series of measurements were taken of the pelvic inclination by a simple inclinometer set on the anterior superior and posterior superior iliac spines in a large series of normal persons. Wiles concludes that the inclination of the pelvis is controlled almost entirely by the muscles surrounding the hip joints. Variations in posture are limited, since the center of gravity must fall within the area occupied by the feet. Two components of faulty posture are commonly seen: (1) alteration in pelvic inclination and (2) changes in dorsolumbar kyphosis. Wiles considers a flat back a postural deformity; instead, moderate lordosis of the upper part of the lumbar region should be sought. Treatment is divided into three stages: (1) restoration of mobility, (2) acquisition of voluntary control of the correction and (3) establishment of new reflexes which will maintain the correct posture.

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[27] Wiles, P.: Lancet **1**:911, 1937.

[Ed. Note.—No universally satisfactory definition of good posture can be formulated. What is meant in simple terms is efficient mechanical use of the body habitually. Most students of this problem will question the accuracy of the author's measurements, believing that pelvic inclination at present is a variable factor, changing with activity and not susceptible to exact measurement by such simple means as he describes. The paper is a distinct contribution to the knowledge of posture and merits careful reading.]

Neoplasm.—Dujovich and Shraer[28] report 2 cases of periosteal lipoma in patients 50 and 60 years old, respectively. Both the tumors, one on the rib and one on the humerus, were extirpated without difficulty, and convalescence was uneventful. This type of tumor is adherent to the periosteum by a pedicule, either primarily or secondarily. As a rule, it is symptomless, as were the tumors observed by the authors. Because of the location, such a growth is at times mistaken for a malignant osseous tumor. It grows slowly, and extirpation is the only method of treatment. The most frequent site is on the skull, next on the femur and then on the vertebral column. A full review of the literature is given.

Roentgen Evidence of Malignant Processes in Bone.—A roentgenographic study of vertebrae affected with metastatic cancer did not show the majority of the osseous lesions. Sections of vertebral bodies were removed by Snure and Maner[29] and replaced with muscle or paraffin; the defects could not be seen in roentgenograms. The majority of the bone markings seen in roentgenograms are due to cortex. The spongiosa may be the site of metastases without being evident roentgenographically. These same destructive changes in the marrow space due to infection may likewise not be visible roentgenographically.

Synovioma.—A detailed report is given by Coley and Pierson[30] of 15 cases of synovioma, with a review of 20 cases from the literature. The tumor described is malignant and occurs in or about the joints. It tends to recur after excision and often to metastasize to the lungs. It may occur at any age. The microscopic appearance is that of an endothelioma or mesothelioma showing typically a villous glandlike appearance. Clinically, the tumor is usually firm, well circumscribed, homogeneous and not particularly tender and occurs frequently near the knee joint. Diagnosis, however, has seldom been made until pathologic examination of the tumor after operation. In the 35 cases reviewed, 30 per cent of the patients survived only five years and 40 per cent only three years. No patient survived more than ten years. The treatment advised is wide excision if the condition is suspected at the first operation, with amputation on recurrence after local removal. Treatment by irradiation is disappointing as this type of tumor is not radiosensitive. Thus far, early treatment appears to have been too conservative, rendering later radical measures ineffectual.

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[28] Dujovich, A., and Shraer, M.: Semana méd. **1**:183, 1937.

[29] Snure, H., and Maner, G. D.: Radiology **28**:172, 1937.

[30] Coley, B. L., and Pierson, J. C.: Surgery **1**:113, 1937.

Fehr[31] adds reports of 4 more cases of synovioma to the 19 reported in the literature (mostly American). He recalls the malignant characteristics of this sarcoma which arises from the synovial tissue of the joint capsule. Only early amputation seems of any permanent value. The tumor grows slowly and metastasizes to the lung.

Epithelial Bone Cysts.—Bissell and Brunschwig[32] add reports of 2 cases of squamous epithelial bone cyst to the 4 reported in the medical literature. Both of his patients gave a history of preceding trauma to the distal portion of the finger in which the cyst subsequently developed. Curettement of the cystic cavity resulted in cure in both patients. The authors believe that these cysts develop from traumatic transplantation of squamous epithelium in or on the bone. An embryonic rest of the epithelium is a possible but less likely cause.

MISCELLANEOUS

Posttraumatic Painful Osteoporosis.—Discussing posttraumatic osteoporosis, Middleton[33] states that the results of sympathectomy are transitory and that ganglionectomy probably offers more hope for beneficial results. He believes that the administration by ionization of certain parasympathetic stimulants, such as carbaminoylcholine, is probably beneficial in the majority of cases in which the condition is persistent.

Osteitis Deformans.—O'Farrell[34] emphasizes the value of the determination of the phosphatase content of the blood in the diagnosis of osteitis deformans. If the normal value for the adult is taken to be 4 units, in cases of Paget's disease the value has occasionally been as much as 130 units. Osteoplastic skeletal metastasis, especially when secondary to prostatic carcinoma, is the only disease of the bone in which such high figures are obtained. In cases of osteitis fibrosa cystica the phosphatase content is seldom above 10 units.

Interosseous Muscles of the Hand.—Salisbury[35] studied the interosseous muscles in 30 hands in order to refute the frequently accepted statement that these muscles are inserted into the base of the proximal and the digital extensor expansion. He finds that the palmar interosseous muscles are inserted, with few exceptions, wholly into the extensor expansion. The first dorsal interosseous muscle is inserted wholly into the proximal phalanx. The other dorsal interosseous muscles are usually inserted into the bases of the proximal phalanges and the expansion, but usually by separate insertions arising from functionally separate portions of the muscle. The separation may be so complete as to form an extrapalmar interosseous muscle. The second dorsal interosseous muscle has a more complete insertion into the proximal phalanx than the fourth, and the fourth more than the third.

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[31] Fehr. A.: Beitr. z. klin. Chir. **165**:88, 1937.

[32] Bissell, A. D., and Brunschwig, A.: Squamous Epithelial Bone Cysts of Terminal Phalanx and Benign Subungual Squamous Epithelial Tumor of the Finger, J. A. M. A. **108**:1702 (May 15) 1937.

[33] Middleton, D. S.: Glasgow M. J. **9**:115, 1937.

[34] O'Farrell, P. T.: Irish J. M. Sc., January 1937, p. 1.

[35] Salisbury, C. R.: J. Anat. **71**:395, 1937.

Urinary Concretions After Skeletal Disease.—Gold [36] calls attention to the often reiterated statement that stones in the renal tract occur in association with abnormal mobilization and excretion of calcium. Thus, renal stones are frequently found in cases of hyperparathyroidism. Even after parathyroidectomy has brought the calcium metabolism back to normal, death from uremia has been observed. The author reports that renal calculi will form in cases of skeletal metastases from mammary carcinoma and multiple myeloma. It is also known that stones will form after an overdose of vitamin D. The formation of renal stones after transverse myelitis is probably due to the associated renal infection.

ORTHOPEDIC OPERATIONS

Arthroplasty of the Knee.—Arthroplasty of the knee was performed on 5 patients by Mocquot and his co-workers.[37] Four of the patients were adults, and 1 was a child of 14 years. In 4 the ankylosis was fibrous and in 1 it was osseous. The condition in all followed acute infectious arthritis, either gonorrheal or pneumococcic. The technic of Putti was used. Postoperative continuous traction with a Kirchner wire was applied. Good functional results were obtained in all. The youngest patient had the least satisfactory result, motion being between 170 and 115 degrees. All were followed for four years or longer.

Arthrodesis of the Knee.—Key [38] describes a method of securing arthrodesis of the knee joint by the use of a large bone peg obtained from the tibial crest. The joint surfaces of the tibia and femur are cut off squarely as in the usual arthrodesis. Cavities extending into the bone are curetted and filled with bone chips. The bone peg, about 4 inches (10 cm.) long and ½ inch (1.3 cm.) thick, is removed from the tibia and driven into the femur. The hole is prepared in the upper end of the tibia with an osteotome, and the peg is shaped into this. The author has not used this operation on children for fear of damaging the epiphyses. He has found this method particularly satisfactory for the treatment of Charcot's arthropathy of the knee.

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[36] Gold, E.: Wien. klin. Wchnschr. **59**:70, 1937.

[37] Mocquot; Boppe, M., and Courvoisier: Rev. d'orthop. **24**:105, 1937.

[38] Key, J. A.: South. M. J. **30**:574, 1937.

Arthrodesis of the Wrist.—The indications for arthrodesis of the wrist are, according to Logròscino,[39] tuberculous osseous lesions, a painful wrist due to arthritis, flaccid paralysis of the extensor muscles and similar conditions. The technic recommended consists of the following procedures: dorsal longitudinal incision of the wrist, separation of the tendons and exposure of the distal 8 cm. of the radius and proximal ends of the second, third and fourth metacarpals and insertion of a graft from 6 to 8 cm. long, obtained with a motor saw from the dorsal third of the radius, under bone flaps raised from the proximal ends of the second, third and fourth metacarpals. The proximal end of the graft is sutured to the radius proper, and the wound is then closed with the wrist in from 30 to 40 degrees of dorsiflexion. The accompanying roentgenograms show satisfactory fusion of the graft, which actually spans the wrist joint.

[Ed. Note.—This procedure is relatively simple but has the fault of most types of purely extra-articular fusion in that the entire strain thrown on the wrist joint subsequent to operation must be borne by the graft.]

Operative Cure for Ingrown Toe-Nail.—Bartlett[40] divides operations for the treatment of ingrown toe-nail into two classes: (1) those which remove a strip of nail and matrix and (2) those in which the wall of the nail is made the site of plastic procedures. Because of the frequency of recurrence and prolonged disability from the usual operative procedures, the author reports a new method of treatment. This consists in the removal of a wedge of tissue from the lateral side of the foot from the base of the nail to a point midway between the tip of the toe and the corner of the nail. The wedge of tissue is ¼ inch wide at the edge of the skin and extends to the bone. When the edges of the skin are approximated, the wall of the nail is pulled away from the nail. The patient walks on the foot after twenty-four hours. The author has had no recurrences of ingrown toe-nail after this operation. Proper shoes are also essential for cure.

FRACTURES AND DISLOCATIONS

Fracture-Dislocation of the Cervical Vertebrae.—Cone and Turner[41] point out that fracture-dislocation of the cervical vertebrae is easily reduced by prompt and appropriate treatment, but reduction can be maintained by a plaster jacket or some other kind of supporting jacket for a time only. When the jacket is removed, deformity may develop shortly after the support is taken away, or the deformity may gradually increase over a period of years until more energetic therapy is provided. In the past four years the authors have obtained fusion in 12 of the 36 patients with injuries to the cervical vertebral column. They feel that satisfactory end-results have been obtained by fusion. Six cases are reported in detail, 3 of fracture-dislocation in the upper cervical region and 3 of fracture-dislocation below the third cervical vertebra. Skeletal traction is applied to the cervical portion of the spine by means of tongs or heavy rustless steel wire through small openings in the skull. This apparatus can be quickly attached to the bed, and a vertical screw arrangement permits the angle of traction to be altered slowly and smoothly. By altering a notch arrangement at the head of the bed, the angle of traction can be changed in order to facilitate reduction. During operation, traction is maintained. Curved bone grafts obtained from a rib or from the ilium are held in place with rustless steel wire. As soon as the wounds permit, fixation of the head, neck and torso is maintained in a plaster cast, and the skeletal traction is removed. Immobilization in a plaster cast should be maintained for six months. When deformities recur after reduction in spite of careful immobilization, fusion is imperative. Another indication for fusion of lesions high in the cervical portion of the spine is paralysis of the muscles of the neck due to cellular involvement of the anterior horn. Fusion immediately protects the patient from recurrence of deformity. In occipitocervical fusion, rotation is lost, but considerable compensatory flexion remains. In this series of cases the patients resumed their previous occupations. The follow-up periods range from nine months to four years. The ages of the patients range from 6 to 72 years. No deaths and no infections of the wound were reported.

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[39] Logròscino, D.: Chir. d. org. di movimento **22**:437, 1937.

[40] Bartlett, R. W.: Conservative Operation for Cure of So-Called Ingrown Toenail, J. A. M. A. **108**:1257 (April 10) 1937.

[41] Cone, W., and Turner, W. G.: J. Bone & Joint Surg. **19**:584, 1937.

Fracture-Dislocation of the Cervical Portion of the Spine.—Roberts[42] reviews the treatment of fractures and dislocations of the cervical portion of the spine, basing his conclusions on 37 patients seen at the Massachusetts General Hospital. Early treatment of such fractures consists of traction with the neck in hyperextension. After reduction, a plaster cast is applied which extends from the top of the head to the pelvis, so that motion in the cervical portion of the spine is prevented. In Roberts' series of patients there were 4 with fracture of the spinous process. Treatment consisted of traction and later fixation in hyperextension. Nonunion without symptoms resulted in 1 patient. There were 5 patients with fracture of the odontoid process. Fixation was maintained for six months. Nonunion without symptoms resulted in 1 patient, and there was 1 death. Twelve patients suffered from fracture of the vertebral body; in six the sixth cervical vertebra was involved. Treatment consisted of hyperextension and traction with an inflated pillow under the shoulders, which was gradually raised until reduction was accomplished. Two patients showed permanent irritation of the nerve root. Nine patients, or 75 per cent. of the patients with fracture showed symptoms due to compression of the cord. In 5 of these damage to the spinal cord was permanent, and death resulted. There were 19 patients with dislocation of cervical vertebrae; only 7 had symptoms referable to the nerves. One death occurred in this group. Operative reduction was attempted on these 19 patients. Open operation is rarely necessary. Treatment for this type of injury consists of immediate reduction and fixation in a plaster cast. For incomplete dislocation, hyperextension and traction alone are sufficient. With the patient under general anesthesia and in the supine position, traction is applied by means of a band of cloth which is passed under the chin and occiput of the patient and is then attached about the waist of the operator. By gentle manipulation, after the method of Walton, the dislocation is reduced. Fixation is maintained for eight weeks, after which exercises are given.

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[42] Roberts, S. M.: J. Bone & Joint Surg. **19**:199 and 477, 1937.

Fracture of the Pelvis.—Rankin[43] reviews the results in 449 fractures of the pelvis treated in four hospitals in Philadelphia from 1907 to 1934. The ages of the patients varied from 1 to 80 years. Sixty-two per cent of the fractures were in males. Thirty-six per cent were due to injuries from automobiles. The fractures of the pelvis tended to be multiple; the ilium and the superior ramus of the pelvis were fractured most commonly. The treatment of choice was suspension in a hammock, with traction on the lower extremities. Treatment varied from simple rest to operative procedures. Seven operations were performed for internal injuries. One hundred and forty-four patients were discharged as well, 249 as improved and 4 as unimproved; 11 were released against advice, and 41 died. Twenty patients died during the first twenty-four hours. Four patients died of shock, 4 of pulmonary edema, 3 of internal injuries and 2 of a ruptured bladder. Only 3 per cent of the patients had severe injuries to the bladder. The other chief disability subsequent to injury was pain in the back or legs. Sixty-seven per cent stated that they were cured six months after injury; 25 per cent had shortening of a leg, which could have been prevented by traction. The average period of total disability in the uncomplicated cases was sixteen and four-tenths weeks. The author advises the early use of physical therapy in treatment.

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[43] Rankin, L. M.: Ann. Surg. **106**:161, 1937.

Conservative Treatment of Fractures of the Leg.—Deuticke and Martys[44] report on 1,070 fractures of the legs treated from 1923 to 1934. Seven hundred and ninety of the fractures involved both bones; 211 of these were compound fractures. There were 109 isolated tibial fractures, 13 of which were compound. One hundred and seventy-one of the fractures included those of children and subperiosteal fractures. The mortality for adults was 2.5 per cent; that in the cases of closed fracture was 1.1 per cent, and in the cases of compound fracture, 6.8 per cent. The authors prefer manual reposition and fixation in an unpadded cast whenever possible. Anatomic reposition went hand in hand with the excellence of the final result. Various complications resulted in the patients (506) treated by extension. Infection developed in 6, necessitating removal of the bone clamps; the infection cleared up in 5 on removal of the clamps, but in 1 incision was necessary. Two patients died of sepsis, possibly due to the use of the clamps. Pulmonary embolism occurred in 4 cases of closed fracture during extension, mostly at the end of the second week of extension. Infarcts of the lungs, which did not prove fatal, occurred in 6 cases during extension. In general, extension delayed union and appeared to increase the chance of pseudarthrosis. It also decreased motion in the joint a trifle. Of 275 patients on whom a bone clamp was used, 15 complained of painful scars at the site. While extension is often indispensable, it should be avoided wherever possible. Of 285 cases of closed fracture pseudarthrosis occurred in 1, while of 90 cases of compound fracture, pseudarthrosis occurred in 5. The femur was amputated in only 1 of 375 cases of fracture of both bones of the leg. In 62 per cent of the cases complete normal function and structure were obtained.

End-Results in Injuries to Epiphyses.—One hundred and six patients with traumatically displaced epiphyses were observed by Lipschultz[45] during a period ranging from sixteen months to eight years after injury. Only a small percentage of these patients were seen less than two years later. This time interval is considered sufficiently long for disturbances of growth to manifest themselves if they are to take place at all. In 15 cases there was roentgenographic evidence of premature ossification and suppression of growth. This group is made up of 6 cases of dislocation of the epiphysis of the radius in which there was retarded growth ranging from 6 to 16 mm., 3 cases in which the epiphyses for the medial epicondyle of the humerus failed to unite after separation, 3 cases in which there was premature ossification with shortening of the ulna, 2 cases in which the proximal epiphysis of the humerus was involved in a similar manner and 1 case in which the separated epiphysis for the lesser trochanter of the femur united, with deformity. In only 3 of these many cases was there noted a light disturbance in function; in these 3 there was separation of the epiphysis of the medial epicondyle of the humerus with nonunion and as a result slight limitation of extension. In all the other cases there was no limitation of motion. The authors conclude that premature ossification with changes in growth takes place frequently after injury to the epiphysis. This condition was found 15 times in the series of 106 cases, or an incidence of 14 per cent, but the amount of shortening was usually minimal and not of clinical significance. Occasionally, however, a case is seen in which the disturbance in growth is marked, resulting in deformity and disturbance of function. This occurs whether or not perfect reduction is obtained and is apparently due to trauma to the epiphysis itself at time of injury.

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[44] Deuticke, P., and Martys, F.: Arch. f. orthop. u. Unfall-Chir. **38**:54, 1937.

[45] Lipschultz, O.: Radiology **28**:223, 1937.

Isolated Fracture of the First Rib.—Betto[46] reports a case of bilateral symmetrical isolated fracture of the first rib. Reports of 2 similar cases were found in the literature. The mechanism of these fractures is discussed at great length. A unilateral fracture of the first rib may follow a severe injury or a blow on the clavicle. On the other hand, Betto believes that bilateral fracture of the first rib occurs when a severe blow or force is applied to the sternum at the moment the scalenus anticus muscles contract violently. In the case reported the injury occurred in an automobile accident, and there was evidence of contusion of the sternum. An associated tear of the pleura with emphysema of the soft tissue has been reported. Therapy consisted in immobilization by strapping to limit respiratory excursion.

Recurrent Dislocation of the Shoulder.—Stefanini[47] describes a method of treatment for recurrent dislocation of the shoulder which has been used in 36 cases, with excellent results in all. The operative technic is as follows: The patient is supine with the arm in abduction. The incision follows the anterior border of the deltoid muscle from the clavicle to the midarm. The greater tuberosity of the humerus is exposed, and a piece of bone is removed to serve as a graft. The coracoid process is then exposed. The fibers of the coracobrachialis muscle are divided, and a bed is made for the graft. The graft is fixed in place with a catgut suture, and the fibers of the muscle are reunited. The wound is closed, and the arm is immobilized in a sling for ten days, after which use is slowly begun.

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46. Betto, O.: Chir. d. org. di movimento **22**:424, 1937.

47. Stefanini, J.: Rev. de chir., Paris **56**:393, 1937.

Hanging Cast for Fracture of the Humerus.—LaFerté and Rosenbaum[48] used the hanging cast in the treatment of fractures of the shaft and neck of the humerus in 58 cases. No comminuted fractures of the head of the femur or fractures involving the condyles were treated by this method. The treatment consists of reduction of the fracture, after which a plaster is applied from the upper third of the humerus to the hand with the elbow at right angles. A plaster wedge is applied to the inner side of the cast just above the elbow to prevent angulation. The cast is carried in a sling. Motion in this at the shoulder and wrist is encouraged. In the cases in which the authors used this method delayed union or nonunion was not observed, and no bad results were encountered. Physical therapy to recover muscular function was necessary in only 20 of the 58 cases. The casts were removed in from five to eight weeks. This type of therapy was first described by Caldwell.[49]

Fracture of the Radius.—Since 1928 the Boehler method of treatment has been used in a total of 873 cases of fracture of the radius at the wrist at Denk's clinic in Vienna.[50] This method consists of reposition with the patient under anesthesia and fixation in an unpadded plaster cast. Certain modifications of this method are practiced; noteworthy is delayed reduction of most fractures. Unless marked displacement is present, the fracture is kept splinted for at least twenty-four hours before reduction is performed. The delay permits swelling to reach a maximum before the cast is applied, according to the authors. The patient is carefully watched for circulatory disturbances. (In 1 of 2 early cases in which the splint was not properly applied, palsy of the ulnar nerve developed, which remained permanently.) In 85 of the cases in the reported series the plaster had to be split. The cast is left for from three to five weeks, union and painless function in the cast comprising the indications for removal. Nonunion of the ulnar styloid process resulted in 152 of 248 cases. Dorsal subluxation of the ulna was observed in 26 and volar subluxation in 9 of the cases in which reexamination was made. The authors agree with others that longer fixation in a long arm plaster cast is indicated but are skeptical about 100 per cent good results. As to results otherwise, good cosmetic and functional results were obtained, if there existed no tendency to axial shifting. When a tendency to shortening of the radius appeared, good function and a poor cosmetic result were obtained. While ideal anatomic reposition is aimed at, it is not an absolute necessity for a good functional result. On the contrary, excellent repositions, as shown roentgenographically, were not always associated with corresponding function. Attempts at reposition after from eight to fourteen days delay healing about two weeks and tend to increase circulatory disturbances. Seven types of fractures about the wrist are listed. The severe intra-articular fractures healed, in general, in twelve weeks, while the transverse fractures healed in from seven to nine weeks.

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[48] LaFerté, A. D., and Rosenbaum, M. G.: Surg., Gynec. & Obst. **65**:231, 1937.

[49] Caldwell, J. A.: Ann. Surg. **97**:161, 1933.

[50] Kotrnetz, H., and Geiringer, F.: Arch. f. Orthop. u. Unfall-Chir. **37**: 504, 1937.

Pseudarthrosis of the Scaphoid Bone of the Hand.—Boerema,[51] of Holland, reports on a group of 36 fractures of the scaphoid bone of the hand. Six of these were old fractures, removal of the ulnar fragment having been done more than ten years before. About half of the fractures (the early ones) had been treated by mobilization. The remaining half (recent fractures) were treated by immobilization in ulnar abduction, according to the method of Boehler. Of 17 patients in whom pseudarthrosis developed, 15 had limitation of volar and especially of dorsal flexion up to 50 per cent of normal. Two had normal range. Seven of the patients were obliged to seek a less arduous occupation because of pain. Two, despite pseudarthrosis, suffered in no way as far as work was concerned. Limitation of motion bore no relation to disability for labor. In short, objective signs were no measure for subjective complaints. The author takes issue with Boehler's absolutely favorable prognosis in this fracture. (Boehler reported 100 per cent union in 150 cases of recent fracture.) However, Boerema is in favor of this type of treatment. He reports spontaneous union in 5 cases without treatment of any sort and reproduces roentgenograms. In 3 of these cases the fractures were incomplete. Of the 6 patients operated on by removal of the ulnar fragment prior to the development of arthritic changes, all but 1 were able to resume full use of the hand, a matter of much surprise to the examiner.

Mallet Finger.—Smillie[52] reports a series of 35 consecutive cases of mallet finger. In recent cases fixation in a plaster of paris cast is employed. A 2 foot (61 cm.) length of dry starched crinoline is rolled into a tube of approximately the same size as the injured finger. One end of the tube is cut on a slant, so that it will fit closely at the web. The tube is slipped over the finger, and the finger and tube are dipped into water. The patient holds the terminal joint in hyperextension and the proximal interphalangeal joint in flexion by pressing the front of the distal end of the finger against the thumb until the plaster dries. The plaster is kept on for at least five weeks. In cases of long standing the ruptured tendon is brought into position and the finger is fixed as before, a sterile plaster bandage and sterile water being used.

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51. Boerema, I.: Arch. f. orthop. u. Unfall-Chir. **38**:42, 1937.

52. Smillie, I. S.: Brit. J. Surg. **24**:439, 1937.

Conservative Therapy for Fracture of the Os Calcis.—Hermann[53] is particularly concerned with that type of fracture of the os calcis in which there is a rather formless comminution of the bone as a whole, with a lateral broadening and pushing up of the posterior part of the heel. The results of treatment in 152 cases of fracture of the os calcis seen in the orthopedic service at the Boston City Hospital are presented. Preliminary treatment consists of the taking of roentgenograms, lateral and axial views of both heels being taken. The film of the uninjured heel is used for a comparison with the measurement of the injured heel and also to detect any bony anomalies. Since in about 10 per cent of the cases fracture of the spine occurs as well, routine roentgenograms of the lower lumbar and thoracic portions of the spine are also taken. The emergency treatment consists of encasing the foot comfortably in a "pillow and sides splint," with appropriate bleb dressing and the use of an ice bag if deemed necessary. A two day preparation of the bone is carried out as soon as the acute local reaction has subsided. This may require from one to ten days. For reduction and fixation, an operating kit is necessary which contains a tightly rolled sterile towel, a sand-bag, a 7 pound (3 Kg.) wooden mallet, a pair of bone tongs and a Forrester bone clamp, a sawed-off crutch, a scapel, sterile dressings and two rolled pieces of silk, 4 by 1¼ inches (10 by 3.2 cm.) in size. The technic is as follows: General or spinal anesthesia is used, and with the patient turned on the side opposite the injury a sand-bag is placed under the inner side of the heel. A tightly rolled towel is placed beneath the external malleolus and with solid blows the piled up bone beneath the external malleolus is pounded down until the normal depression between the external malleolus is restored. Next, with the scapel small stab wounds are made in the upper posterior part of the heel, and the tongs are driven in and locked. The crutch is used for countertraction, the handle resting against the operator's abdomen or chest and the cross bar of the sawed off portion resting against the sole of the foot in the line of the calcaniocuboid and the astragaloscaphoid joints. Traction is maintained by means of the tongs to overcome the pull of the muscles of the calf. The tongs are then removed, and the heel is remolded by the use of the Forrester bone clamp. When the desired compression has been obtained, traction is again applied through this clamp. The entire heel is carefully molded in this fashion. Roentgenograms are taken. The tongs are removed and a low plaster of paris cast is applied with the foot in slight inversion and in extreme plantar flexion. While the cast is hardening, manual pressure is applied over the pads beneath the malleoli. The first cast is removed in two weeks. The malleolar pads are then carefully replaced, and with the foot at right angles a new cast is applied.

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[53] Hermann, O.: J. Bone & Joint Surg. **19**:709, 1937.

This is repeated every two weeks for from ten to twelve weeks in order to maintain constant pressure beneath the malleoli, which retards callus formation. After removal of the last cast, a special ambulatory splint is applied at once. Physical therapy is then instituted. Full weight bearing without crutches but with the ambulatory splint is begun ten days or two weeks after omission of the last cast. Six weeks later, or four and one-half months after the initial reduction, the ambulatory splint is removed. If the patient complains of persistent pain in the region of the subastragalar joint and the original fracture was of the interarticular type and comminuted, then and only then is fusion of the subastragalar joint considered. The results in the 152 cases studied have been divided into good, fair and poor. Good results were obtained in 111 cases, or 75 per cent; fair results in 21 cases, or 14 per cent, and poor results in 20 cases, or 13 per cent. The patients with good results were those who by the sixth or seventh month had regained full functional use of the injured heel and had no pain or discomfort in any part of the heel after normal activity.

Treatment of Pseudarthrosis; Result of Ten Years' Experience.—In a statistical report on 181 cases of pseudarthrosis of the long bones in which operation was performed, Pfab[54] notes that healing occurred in 157 and that it had not taken place in 24. Various methods were employed (drilling, step formation with bone fixation, sliding bone grafts with fixation with kangaroo tendons and wire). Pseudarthrosis developed in 69, or 9.4 per cent, of 7,296 cases of fracture seen over a ten year period. Twenty-three of the author's 69 personal cases of pseudarthrosis occurred in a total of 400 cases of open fracture, while 46 occurred in a total of 6,896 cases of closed fracture.

Planes of Displacement and Zones of Destruction in Fractures.—Haase[55] reports another case of "gradual fracture," this time of the clavicle in a 47 year old worker, and attributes it to the fatigue of bone. Just as the structure of inanimate materials are injured by overloading, tensions and strains, so the structure of bone undergoes changes when its physical characteristics are insufficient to resist the stresses applied. When an aluminum strap is pulled apart, the tear is at an angle of 45 degrees to the axis of pull, and stress lines appear at right angles to the tear as well. When bone or wood blocks are subjected to compression, oblique fracture planes occur at an angle of about 45 degrees to the long axis of compression. Also, distant changes occur in the physical structure apart from the immediate zone of fracture. Even when not directly visible, injuries to the capillary structure of bone must accompany these distant changes. These disturbances may later make their appearance clinically. Close roentgenographic study of the shafts distant from the site of fracture will occasionally give evidence of such damage.

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[54] Pfab, B.: Arch. f. orthop. u. Unfall-Chir. **38**:90, 1937.

[55] Haase, W.: Arch. f. orthop. u. Unfall-Chir. **37**:592, 1937.

The Effect of the Electrolysis of Metals on the Bone.—Venable and his co-workers,[56] after a study of the electrolysis of various metals in the tissues, came to the following conclusions: It is impossible from macroscopic, microscopic and roentgenographic studies to determine the reactions of soft tissues and bone to metals. Electrical force is generated when different metals are placed in tissues, the amount of electric current produced being dependent on the difference in potential of the metals and the distance between the poles. Pure metals alone are inert. Any reaction about them is wholly chemical. Any appliance of galvanized iron, plated steel or metallic alloy causes some galvanic action. In the selection of alloys, those containing iron show the greatest reaction. Chromium is readily liberated on plating and is very toxic. The authors suggest that an alloy similar to vitalium in which vanadium may be substituted for the chromium be used for bone work.

Serum Phosphatase in Diseases of Bone.—Mitchell and Crawford[57] review the literature pertaining to the clinical application of serum phosphatase to diseases of the bone and, in addition, present an analysis of the readings taken in several hundred cases of osseous lesions. Their results show that in general there is an increase in activity of the serum phosphatase accompanying the formation of unusual amounts of new or of abnormal bone. There appears to be little or no increase associated with the purely destructive lesion of bone. Determinations of serum phosphatase are important aids in the diagnosis and differential diagnosis of Paget's disease, osteitis fibrosa cystica and tumors of bone. The level of the activity of the serum phosphatase cannot be used as an index of healing or of the ability of a fracture to heal. No significant changes in the activity of serum phosphatase were noted in cases of tuberculosis of the bones and joints and of osteomyelitis. Determinations of the serum phosphatase are suggested as a criterion of effective therapy in Paget's disease, hyperparathyroidism, osteoblastic osteogenic sarcoma and rickets.

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[56] Venable, C. S.; Stuck, W. G., and Beach, A.: Ann. Surg. **105**:917, 1937.

[57] Mitchell, C. L., and Crawford, R. R.: J. Bone & Joint Surg. **19**:630, 1937.

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